Pharmacologic Treatment of Obesity in Adults: Standards of Care in Overweight and Obesity

*American Diabetes Association Professional Practice Committee for Obesity**

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Obesity medications may be part of a comprehensive care plan for adults with obesity. The Obesity Association, a division of the American Diabetes Association (ADA), developed comprehensive, evidence-based guidelines on the pharmacologic treatment of obesity in adults. When used in conjunction with lifestyle modifications, obesity medications have demonstrated efficacy in inducing and sustaining weight reduction while concurrently improving clinical outcomes of obesity and obesity-related diseases and complications. Health care professionals should engage people with obesity in a person-centered, shared decision-making approach when selecting an obesity medication to optimize health outcomes while emphasizing individual needs and preferences. The ADA's Obesity Association encourages health care professionals to adopt these guidelines for treatment of obesity in adults.

Obesity medications are an essential component of a comprehensive approach to obesity management, offering significant benefits beyond lifestyle interventions alone for many people. Research indicates that pharmacotherapy can lead to greater weight reduction and improved weight maintenance than placebo in adults with obesity (1). Of note, randomized controlled trials (RCTs) of obesity medications include lifestyle intervention in both placebo and study drug arms, which most typically comprises a 500-calorie deficit meal plan and behavioral intervention that usually produces 2.6% weight reduction in the placebo group (2), and the placebo group receives a placebo pill or injection, as appropriate. In meta-analyses of RCTs, people treated with obesity medications experienced substantial weight reduction compared with placebo (2,3). Participants treated with obesity medications also had improvements in cardiometabolic markers, such as glycemia and lipid profiles (2,3), and some obesity medications demonstrated improvements in cardiovascular outcomes and other obesity-related diseases (4–7). When used appropriately, obesity medications offer a favorable risk-benefit profile in many cases, making them a viable option for many people with obesity.

Multiple weight-regulating hormones change in response to weight reduction, creating a physiologic environment conducive to the body returning to its higher prior weight (8,9). Weight reduction also negatively affects energy expenditure and basal metabolic rate, which makes weight-loss maintenance challenging for individuals with obesity (10,11). However, obesity medications enhance the ability to reduce weight and maintain weight reduction over extended periods (12), and many target the dysregulated neurohormonal systems that cause weight gain and prevent sustained weight reduction (13). Over the past few decades, substantial progress has been made regarding the efficacy and safety of obesity medications (14), and multiple obesity medications are now available that result in sustained weight reduction and improvements in multiple obesity-related diseases and complications. By discussing and considering obesity medications for adults with obesity, health care professionals can offer an effective treatment strategy that addresses overall health where treatment goals extend beyond weight reduction to include improving obesity-related diseases and complications, physical function, and well-being.

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*A complete list of members of the American Diabetes Association Professional Practice Committee for Obesity can be found in the appendix at the end of the article.

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The methodology for the "Standards of Care in Overweight and Obesity" has been described previously (15). These guidelines are developed by the American Diabetes Association (ADA) Professional Practice Committee for Obesity, an interprofessional team of experts. Subcommittees conduct systematic literature reviews to inform updates, guided by a methodologist and librarian. Recommendations are graded based on evidence quality (A, B, C, or expert opinion E) with the strongest evidence derived from large, well-designed RCTs. While evidence forms the basis, recommendations emphasize person-centered care. Recommendations are deliberated by Professional Practice Committee voting members, with an 80% consensus required for approval. External peer reviews and adherence to established guideline development principles ensure credibility and rigor in this approach. Of note, this section uses the term obesity medications; the terms obesity management medications and anti-obesity medications may also be used in the literature to refer to these medications.

This section includes only medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity among individuals with obesity or individuals with overweight and the presence of at least one obesity-related disease or complication. It does not include medications without an approved indication for obesity (e.g., metformin), medications FDA-approved to treat rare genetic conditions associated with obesity (e.g., setmelanotide for Bardet-Biedl syndrome), or FDA-approved devices to treat obesity (e.g., oral cellulose–citric acid hydrogel).

Discussing Obesity Medications

Recommendations

2.1 Select obesity medications using a person-centered approach that incorporates shared decision-making and is grounded in the best available evidence **B**.

2.2 Prioritize obesity medications most likely to achieve and maintain intended treatment goals while considering cost, access, tolerability, risk for adverse effects, and individual preferences **A**.

2.3 Nutrition, physical activity, and behavioral therapy should be used in combination with obesity medications to achieve health goals **A**.

2.4 Whenever clinically appropriate, minimize use of weight-promoting medications used to treat other conditions, particularly among adults with obesity **A**.

Shared decision-making fosters a collaborative partnership between health care professionals and individuals with obesity, integrating person-specific factors (e.g., goals, values, and preferences) into the decision-making process. In general, shared decision-making reduces decisional conflict, improves individuals' knowledge of diseases and treatment options, and increases satisfaction with treatment decisions (16,17). For example, a meta-analysis (18 RCTs) showed that shared decision-making for cardiovascular risk management improved hemoglobin A1c (A1C) (17). Future work is needed to design shared decision-making tools specific to obesity medications.

As obesity medications induce clinically meaningful weight reduction relative to placebo (2,18), the choice of therapy should prioritize medications most likely to improve obesity-related diseases and complications and to achieve and maintain weight reduction goals. Therefore, this section outlines an approach focused on reducing risk of and burden from obesity-related diseases rather than solely focusing on weight reduction goals. Table 2.1 contains a summary of treatment and weight-reduction outcomes as well as adverse effects reported in RCTs of obesity medications. The risk of medication-related adverse effects should be evaluated for each individual, as this risk may vary depending on their medical history and concomitant medications. In a network meta-analysis (132 RCTs), adverse events leading to drug discontinuation were significantly higher for all obesity medications compared with placebo (2). Health care professionals should present the potential benefits, risks, and expected outcomes of obesity medications. Medication selection should be guided by person-centered factors, including evidence, treatment burden, costs, and individuals' therapeutic goals and preferences.

Behavioral Lifestyle Therapy With Obesity Medications

Nutrition, physical activity, and behavioral therapy must be components of all comprehensive obesity treatment plans, including those with obesity medications. The efficacy of obesity treatment interventions that include nutrition and physical activity have been documented in meta-analyses (1,19,20), and the addition of obesity medications to lifestyle interventions improves weight reduction and weight-loss maintenance (1,19,21).

Greater weight reduction may be achieved when a lifestyle behavioral modification program is administered with an obesity medication among individuals with obesity (22–25). For example, in a 1-year RCT, participants in a naltrexone-bupropion plus intensive behavioral program group lost 9.3% of baseline weight compared with 5.1% in the placebo plus intensive behavioral program group (22). The degree of weight reduction achieved is related to program intensity (20), and engagement in behavioral components is also associated with greater weight reduction (26). Some obesity medications are associated with increased fullness as well as decreased hunger, food preoccupation, dietary disinhibition, and binge eating compared with placebo (27,28), which may aid individuals in achieving and sustaining the lifestyle treatment plan.

Weight-Promoting Medications

Before prescribing an obesity medication, health care professionals should carefully review individuals' concomitant

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TABLE 2.1 Summary of features of FDA-approved obesity medications influencing medication selection

Medication	Contraindications	Placebo-subtracted weight reduction in meta-analysis*	Effects on obesity-related diseases and complications†	Estimated costs‡	Common adverse effects	Strategies to manage adverse effects§	Clinical suggestions and monitoring
Orlistat	• Malabsorption • Cholestasis	3.1%	Demonstrated benefit • BP Potential benefit • T2D	Moderate	• Oily fecal spotting • Oily stools • Flatulence • Fecal urgency • Increased defecation	• Follow low-calorie meal plan with <30% of calories from fat to reduce GI effects • Avoid high-fat meal plan, as it increases adverse effects (e.g., ketogenic, low-carbohydrate)	• Advise that GI adverse effects typically subside within 4 weeks • Use MVI containing fat-soluble vitamins at bedtime to avoid deficiencies
Phentermine	• CVD • Uncontrolled HTN • Glaucoma • Hyperthyroidism • SUD • Agitated states	3.6%	Unknown	Low	• Dry mouth • Insomnia • Headache • Irritability • Constipation	• Adequate water and dietary fiber intake to manage dry mouth and constipation • Avoid taking medication in the evening to reduce insomnia	Monitor • Heart rate and BP for increases with initiation and dose escalation
Phentermine-topiramate	• CVD • Uncontrolled HTN • Glaucoma • Hyperthyroidism	8.8%	Potential benefit • T2D • BP • OSA	Moderate	• Paresthesia • Dry mouth • Headache • Constipation • Insomnia • Altered taste • Cognitive impairment	• Adequate water intake to manage dry mouth, constipation, and reduce risk of kidney stones • Adequate fiber intake to manage constipation • Take medication in the morning to reduce insomnia • Paresthesia or cognitive changes, if bothersome, may improve with reduced dose	• Advise people of childbearing potential of teratogenicity and counsel on need for effective contraception Monitor • Heart rate and BP for increases with initiation and dose escalation • Mood changes • Electrolytes for changes in renal function
Naltrexone-bupropion	• Uncontrolled HTN • Seizure disorders • Glaucoma • Anorexia or bulimia • SUD • Chronic opioid use	4.8%	Potential benefit • T2D No benefit • BP	Moderate	• Nausea • Constipation • Vomiting • Headache • Dizziness • Dry mouth	• Reduce portion size to manage nausea • Adequate water and dietary fiber intake to manage dry mouth and constipation • Administer evening dose at least 3 h before bedtime to reduce insomnia • Avoid high-fat meal plan, as it increases adverse effects (e.g., ketogenic, low-carbohydrate)	Monitor • BP for increases with initiation and dose escalation • Mood changes
Liraglutide	• Severe GI disease • Personal or family history of medullary thyroid carcinoma or MEN type 2	4.5%	Demonstrated benefit • T2D‖ Potential benefit • BP • ASCVD • MASH • OSA • OA	High	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate	• Reduce portion size to manage nausea • Adequate water and dietary fiber intake to manage constipation • Last meal at least 2 h before bedtime to reduce dyspepsia	• Rotate injection site location to reduce pain • Refrigerate medication • Advise people on concurrent insulin or sulfonylureas of hypoglycemia risk Monitor • Heart rate • Mood changes

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TABLE 2.1 Summary of features of FDA-approved obesity medications influencing medication selection (Continued)

Medication	Contraindications	Placebo-subtracted weight reduction in meta-analysis*	Effects on obesity-related diseases and complications†	Estimated costs‡	Common adverse effects	Strategies to manage adverse effects§	Clinical suggestions and monitoring
Semaglutide	• Severe GI disease • Personal or family history of medullary thyroid carcinoma or MEN type 2	11.9%	Demonstrated benefit • T2D‖ • BP • ASCVD‖ • HFpEF • MASH‖ • OA	High	• Nausea • Vomiting • Diarrhea • Constipation • Dyspepsia • Headache • Fatigue • Increased heart rate	• Reduce portion size and dietary fat to manage nausea • Adequate water and dietary fiber intake to manage constipation • Last meal at least 2 h before bedtime to reduce dyspepsia	• Rotate injection site location to reduce pain • Refrigerate medication • Consider MVI daily to avoid micronutrient deficiencies • Advise people with T2D of diabetic retinopathy risk • Advise people on concurrent insulin or sulfonylureas of hypoglycemia risk Monitor • Heart rate • Mood changes • Symptoms of cholelithiasis • Electrolytes for changes in renal function
Tirzepatide	• Severe GI disease • Personal or family history of medullary thyroid carcinoma or MEN type 2	16.2%	Demonstrated benefit • T2D‖ • BP • OSA‖ Potential benefit • ASCVD • HFpEF • MASH • OA	High	• Nausea • Vomiting • Diarrhea • Constipation • Dyspepsia	• Reduce portion size and dietary fat to manage nausea • Adequate water and dietary fiber intake to manage constipation • Last meal at least 2 h before bedtime to reduce dyspepsia	• Rotate injection site location to reduce pain • Refrigerate medication • Consider MVI daily to avoid micronutrient deficiencies • Advise people on concurrent insulin or sulfonylureas of hypoglycemia risk Monitor • Mood changes • Symptoms of cholelithiasis • Electrolytes for changes in renal function

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; MASH, metabolic dysfunction–associated steatohepatitis; MEN, multiple endocrine neoplasia syndrome; MVI, multiple vitamin and mineral; OA, osteoarthritis; OSA, obstructive sleep apnea; SUD, substance use disorder; T2D, type 2 diabetes. *Values reflect placebo-subtracted mean percent weight loss estimated in meta-analyses to represent the weight reducing effect of the obesity medication beyond that achieved with lifestyle change alone (51,52). These meta-analyses include individuals with obesity both with and without obesity-related diseases and complications. Lifestyle counseling achieved 2.6% weight reduction in meta-analyses (2). Given that obesity medications should be used in combination with lifestyle changes, the total anticipated weight reduction effect would be the combined effect of the obesity medication plus lifestyle (e.g., 3.1% for orlistat plus 2.6% for lifestyle counseling would total 5.7% anticipated weight loss). Intensive behavioral therapy typically results in greater magnitude of weight reduction relative to lower intensity lifestyle counseling; therefore, the combination of obesity medication with intensive behavioral therapy may result in greater total anticipated weight reduction effect. Individual responses to obesity treatment may vary. †Obesity-related diseases and complications considered include T2D, BP, MACE, HFpEF, MASH, OSA, and OA. Obesity medications with A-level evidence of beneficial outcomes identified as "demonstrated benefit" for outcomes related to the specified condition, whereas those with B- or C-level evidence of beneficial outcomes identified as "potential benefit." "No benefit" indicates that there is evidence of no beneficial effects on the outcome. If an outcome for one of the obesity-related diseases or complications is not listed, then the effect on this condition is unknown (i.e., there is no evidence evaluating the obesity medication on the outcome). ‡Individuals may experience cost barriers in accessing obesity medications due to a lack of insurance coverage, high copays, or other high out-of-pocket costs. Information presented in this column represents estimated out-of-pocket costs without insurance and using discount programs available from the manufacturer. "Low" is defined if estimated costs are less than $100/month, "moderate" if $100-$200/month, or "high" if greater than $200/month. Actual costs for the individual obtaining the medication may differ from these estimates. §Most adverse effects will improve with reduction in obesity medication dose, and a slow dose escalation may reduce the likelihood of adverse effects and improve tolerability. Not all individuals need the maximum approved dose of the medication. ‖These are medications currently FDA-approved for the treatment of the identified obesity-related disease or complication.

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medications, as studies have found that medications that promote weight gain are commonly used, including among individuals with obesity (29–31). Health care professionals should be aware of weight-promoting medications (Table 2.2) (32). As the number of prescribed weight-promoting medications increases, individuals' BMI and waist circumference are more likely to have greater increases over time (33). In addition, studies have found that participants using weight-promoting medications have reduced weight-loss efficacy with lifestyle interventions to treat obesity (34,35).

Whenever possible and clinically appropriate, avoid initiating a prescription for weight-promoting medications among individuals with obesity and instead select a non-weight-promoting alternative. For example, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics should be prioritized to treat hypertension rather than some β-blockers, as these options are weight-neutral rather than weight-promoting. When diabetes medications are needed for glycemic management, medications most likely to cause weight gain should be discouraged in favor of alternatives that are non-weight-promoting (Table 2.2). However, health care professionals should not refrain from prescribing weight-promoting medications when needed to achieve treatment goals for that condition (e.g., blood pressure in hypertension).

For individuals with obesity who may already be using weight-promoting medications, health care professionals should determine whether a dose reduction or non-weight-promoting alternative may be clinically appropriate. If so, individuals should be engaged in determining whether their medication plan should be modified, accounting for the benefits and risks of all treatment options. Health care professionals should be aware that cessation of weight-promoting medications does not necessarily result in weight reduction. For individuals who must remain on weight-promoting medications, obesity medications may be beneficial in achieving treatment and weight goals.

Setting Treatment Goals With Obesity Medications

Recommendations

2.5a Treatment goals should be incremental and individualized, based on the severity of obesity, obesity-related diseases and complications, and individuals' needs, life circumstances, and preferences **E**.

2.5b Aim for a sustained reduction in baseline body weight of ≥5% for adults treated with obesity medications, which may achieve some clinically meaningful health benefits **A**. Aim for a sustained weight reduction of ≥10% to manage many obesity-related diseases or complications **A**; in some cases, a ≥15% weight reduction may be indicated to achieve greater therapeutic benefit **B**.

Obesity is a heterogeneous disease with varying effects on health, necessitating individualized treatment plans. Sociocultural factors and personal motivation also play a critical role in treatment goals. Culturally tailored interventions that respect individual preferences and lived experiences, rather than those that impose rigid weight-loss goals, are needed. Health care professionals should evaluate each individual for obesity-related diseases and complications as well as physical symptoms, psychological symptoms, functional limitations, and impact on well-being due to excess adiposity (36,37). Such a holistic assessment will highlight the need for tailored treatment goals, as health risks and weight-reduction benefits vary by the severity of obesity and its related diseases and complications. Health care professionals should be aware that the typical time course to achieve treatment goals varies between individuals; therefore, reevaluation every 3 months may be useful to monitor progress.

Achieving a ≥5% reduction in baseline body weight for adults treated with obesity medications is associated with health benefits (18,38–42). Research demonstrates that a 5% weight reduction improves cardiometabolic risk factors (2,43,44). For example, the CONQUER RCT demonstrated that over 60% of participants treated with phentermine-topiramate achieved ≥5% weight reduction as compared with 21% with placebo, and weight reduction was accompanied by improvements in metabolic risk factors (40). In the SURMOUNT-1 RCT, over 85% of participants who received tirzepatide achieved a ≥5% reduction goal compared with 35% with placebo; notable improvements in cardiometabolic measures were also observed (18).

For individuals with obesity-related diseases and complications, achieving ≥10% reduction in baseline body weight has consistently demonstrated improvements in these conditions. In general, 10–15% weight reduction results in significantly greater improvements in glycemia, blood pressure, and lipids compared with 5–10% loss (45). In most cases, the magnitude of weight reduction is directly proportional to risk factor improvements; therefore, sustained weight reduction of ≥10% is often required for optimal cardiometabolic benefits. Obesity-related diseases and conditions that benefit from this weight-loss magnitude include metabolic dysfunction–associated steatohepatitis with moderate-to-severe fibrosis (7,46), heart failure with preserved ejection fraction (47,48), and knee osteoarthritis (49).

Emerging data suggest that ≥15% weight reduction may be needed to achieve clinical benefits in some cases (45), particularly for individuals with moderate-to-severe obesity-related conditions. In the SURMOUNT-OSA trial, participants with obesity and moderate-to-severe obstructive sleep apnea who received tirzepatide achieved mean weight reduction exceeding 15% and experienced significant reductions in the apnea-hypopnea index (AHI), hypoxic burden, and systolic blood pressure compared with placebo (6). A meta-analysis found a dose-response relationship between AHI and weight

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TABLE 2.2 Weight-promoting medications and alternatives

Condition	Weight-promoting medications	Non-weight-promoting alternatives
Hypertension	α-Blockers Metoprolol Propranolol Atenolol	ACE inhibitors ARBs Carvedilol Nebivolol Thiazide and thiazide-like diuretics
Diabetes	Insulin Sulfonylureas Thiazolidinediones	α-Glucosidase inhibitors Metformin* GLP-1 receptor agonists* Dual GIP and GLP-1 receptor agonist* SGLT2 inhibitors* Vidagliptin* Sitagliptin* Other DPP-4 inhibitors Pramlintide*
Contraception	Depo-medroxyprogesterone acetate Progestins	Copper IUDs Barrier contraceptive methods
Allergies	Diphenhydramine Cetirizine Hydroxyzine Fexofenadine Meclizine Cyproheptadine	Loratadine
Depression	Nortriptyline Doxepin Amitriptyline Imipramine Phenelzine Paroxetine Escitalopram Citalopram Fluoxetine† Sertraline† Mirtazapine	Bupropion*
Psychosis	Clozapine Olanzapine Risperidone Quetiapine Perphenazine Aripiprazole	Ziprasidone
Mood instability	Lithium	Ziprasidone Lamotrigine
Epilepsy	Gabapentin Pregabalin Valproic acid Vigabatrin Carbamazepine	Lamotrigine Levetiracetam Phenytoin Topiramate* Zonisamide* Felbamate*
Inflammation	Glucocorticoids	NSAIDs
Other	Megestrol acetate	

This table was adapted with permission from *Clinical Management of Obesity*, 3rd edition (260). ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; IUD, intrauterine device; NSAID, nonsteroidal anti-inflammatory drug; SGLT2, sodium–glucose cotransporter 2. *Alternative medication is associated with weight reduction; otherwise, alternative medications are considered weight neutral. †Short-term use of less than 12 months is typically weight neutral, while long-term use is associated with weight gain.

change (6), where a 20% weight reduction lowers AHI by 57% and a 30% weight reduction lowers AHI by nearly 70%.

Ultimately, individualized goals should be determined based on a comprehensive assessment, including disease severity, risk-benefit considerations, motivation, and personal circumstances. While weight-reduction goals of ≥15% may be beneficial for some individuals with moderate-to-severe obesity-related diseases, others may experience meaningful health improvements with less weight reduction. Personalized treatment strategies may lead to long-term success and sustainability.

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Selecting Obesity Medications

Recommendations

2.6a In adults with obesity who do not have obesity-related diseases or complications, consider obesity medications as part of the treatment plan to promote weight reduction, prevent further weight gain, and reduce the risk of developing obesity-related diseases and complications **A**, **C** (Fig. 2.1).

2.6b Obesity medications should be offered as part of initial treatment for obesity to adults with or at high risk of obesity-related diseases or complications **A**.

2.7 In adults with overweight or obesity and prediabetes, the treatment plan should prioritize obesity medications with demonstrated evidence for preventing progression to type 2 diabetes **A**, **B** (Fig. 2.2).

2.8 In adults with overweight or obesity and type 2 diabetes, the preferred obesity medication should be a glucagon-like peptide 1 receptor agonist (GLP-1RA) or a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist (dual GIP/GLP-1RA) given their weight reduction and glucose-lowering efficacy **A**. If a preferred obesity medication is unable to be used, other obesity medications with demonstrated glucose-lowering efficacy may be considered within the context of their risks and adverse effects **B** (Fig. 2.2).

2.9 In adults with overweight or obesity and essential hypertension, the treatment plan should prioritize obesity medications with demonstrated blood pressure reduction benefit **A**, **B** (Fig. 2.2).

2.10 In adults with overweight or obesity and established atherosclerotic cardiovascular disease, the treatment plan should include a GLP-1RA with demonstrated benefits **A**, **B** or a dual GIP/GLP-1RA with potential benefits in reducing cardiovascular events **B** (Fig. 2.2).

2.11 In adults with overweight or obesity and heart failure with preserved ejection fraction, the treatment plan should include a GLP-1RA or dual GIP/GLP-1RA with demonstrated improvements in heart failure-related symptoms **A** or reduction in heart failure events **A**, **B** (Fig. 2.2).

2.12 In adults with overweight or obesity and metabolic dysfunction–associated steatohepatitis (MASH) with moderate or advanced fibrosis, the treatment plan should include a GLP-1RA or a dual GIP/GLP-1RA with demonstrated or potential benefits on MASH **A**, **B**, **C** (Fig. 2.2).

2.13 In adults with overweight or obesity and moderate-to-severe obstructive sleep apnea, the treatment plan should prioritize obesity medications with demonstrated improvements in sleep apnea **A**, **B**, **C** (Fig. 2.2).

2.14 In adults with overweight or obesity and moderate osteoarthritis, the treatment plan should prioritize a GLP-1RA or dual GIP/GLP-1RA with potential improvements in osteoarthritis symptoms **B**, **C** (Fig. 2.2).

The FDA has approved several obesity medications as adjuncts to a reduced-calorie meal plan and increased physical activity in individuals with obesity or individuals with overweight and the presence of at least one obesity-related disease or complication. Historically, label-defined eligibility criteria were BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with one or more obesity-related disease or complication; however, these thresholds are no longer included in the labels of several obesity medications (i.e., phentermine-topiramate, liraglutide, semaglutide, and tirzepatide). Table 2.3 describes the mechanisms of action and dosing for all FDA-approved obesity medications. Most obesity medications are approved for long-term treatment; the exception is monotherapy with phentermine or other adrenergic agents (e.g., diethylpropion) that were approved for short-term use. Obesity medications are invaluable components of initial treatment in adults who already have or who are at high risk of developing obesity-related diseases or complications, as they can significantly mitigate the progression of these conditions (4,6,47,48). If individuals with obesity-related diseases or complications initially decline obesity medication, it may be appropriate to reevaluate their interest in this treatment option at follow-up.

All FDA-approved obesity medications have demonstrated weight-reduction efficacy in clinical trials (18,38–42,50). In a network meta-analysis, in comparison with placebo at study end point, orlistat was associated with 3.1% greater weight reduction (22 RCTs), phentermine-topiramate was associated with 8.8% greater weight reduction (5 RCTs), naltrexone-bupropion was associated with 4.8% greater weight reduction (2 RCTs), liraglutide was associated with 4.5% greater weight reduction (10 RCTs), semaglutide was associated with 11.9% greater weight reduction (13 RCTs), and tirzepatide was associated with 16.2% greater weight reduction (6 RCTs) (51). Of note, these meta-analyses include RCTs of adults with obesity who do and do not have obesity-related diseases and complications, and other network meta-analyses have reported similar results (2,3).

To date, phentermine has only been studied in short-term RCTs (28 weeks or less) (50,52–54); however, a 2019 observational study demonstrated that long-term phentermine use was associated with significant weight reduction: individuals prescribed the medication for $\geq$12 months experienced a 7.4% greater weight reduction compared with those with $\leq$3 months (55). This analysis also showed no significant increase in the risks of cardiovascular disease or death among individuals prescribed phentermine long term. In individuals without cardiovascular disease, serious psychiatric disease, or substance use disorder, phentermine monotherapy may be an effective and safe option for achieving sustained weight reduction, with the caveat that no long-term efficacy and safety trial data currently exist (56,57). Long-term phentermine monotherapy is an off-label use, as this medication is only FDA-approved for short-term use, and health care professionals should be aware that some geographic areas may legally restrict this approach. Long-term phentermine monotherapy may be considered after discussion of the benefits and risks of all obesity

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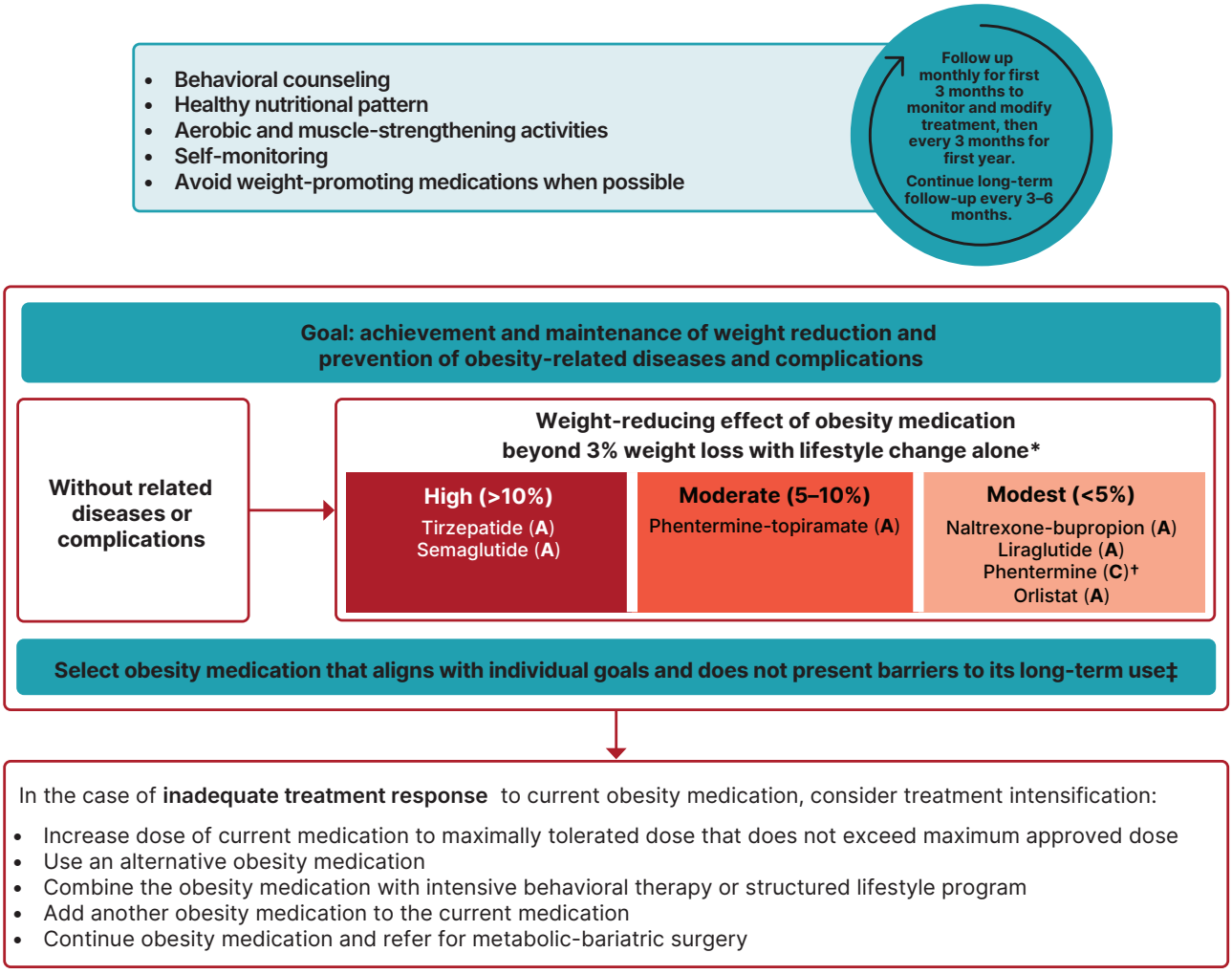
Behavioral counseling
Healthy nutritional pattern
Aerobic and muscle-strengthening activities
Self-monitoring
Avoid weight-promoting medications when possible
Follow up monthly for first 3 months to monitor and modify treatment, then every 3 months for first year.
Continue long-term follow-up every 3–6 months.
Goal: achievement and maintenance of weight reduction and prevention of obesity-related diseases and complications
Without related diseases or complications
Weight-reducing effect of obesity medication beyond 3% weight loss with lifestyle change alone*
High (>10%)
Tirzepatide (A)
Semaglutide (A)
Moderate (5–10%)
Phentermine-topiramate (A)
Modest (<5%)
Naltrexone-bupropion (A)
Liraglutide (A)
Phentermine (C)†
Orlistat (A)
Select obesity medication that aligns with individual goals and does not present barriers to its long-term use‡
In the case of inadequate treatment response to current obesity medication, consider treatment intensification:
Increase dose of current medication to maximally tolerated dose that does not exceed maximum approved dose
Use an alternative obesity medication
Combine the obesity medication with intensive behavioral therapy or structured lifestyle program
Add another obesity medication to the current medication
Continue obesity medication and refer for metabolic-bariatric surgery

FIGURE 2.1 Obesity medications among adults without obesity-related diseases or complications. Among adults without obesity-related diseases or complications, obesity medications are indicated in adults with obesity. *The level of evidence ratings are identified in parentheses. Obesity medications are listed in relative order of benefit within each box where medications with greatest magnitude of benefit are listed first, although most obesity medications have not been compared in direct head-to-head trials. Categorization reflects expected average placebo-subtracted weight loss in meta-analyses to represent the weight-reducing effect of the obesity medication beyond that achieved with lifestyle change alone (51,52). Individual responses may vary. Given that obesity medications should be used in combination with lifestyle changes, the total anticipated weight reduction effect would be the combined effect of the obesity medication plus lifestyle (e.g., >13% loss for high weight-reducing effect obesity medication plus lifestyle). In meta-analyses, lifestyle counseling achieved 2.6% weight reduction (2); however, intensive behavioral therapy typically results in greater magnitude of weight reduction relative to lower intensity lifestyle counseling. Therefore, the combination of obesity medication with intensive behavioral therapy may result in greater total anticipated weight reduction effect. Of note, the maximum dose of semaglutide and liraglutide approved to treat obesity differs from the doses of these medications approved to treat type 2 diabetes. †To date, phentermine has only been studied in short-term RCTs (≤6 months duration). ‡Barriers to long-term use may include adverse medication effects, insurance coverage, out-of-pocket costs, etc.

medications, including those FDA-approved for long-term use. Phentermine is a schedule IV controlled substance, and therefore health care professionals should perform an in-person examination and evaluation, preferably with electrocardiogram, prior to prescribing this medication. The starting dose of phentermine should be 15 mg daily or less, and the dose may be increased based on tolerability and treatment response. Health care professionals should consider monthly follow-up, including monitoring of blood pressure and pulse, until the phentermine dose is stable, with follow-up every 3–6 months for long-term treatment to maintain health goals. Phentermine is one of the most prescribed obesity medications in the U.S. (58).

Prior research has shown that adverse effects from obesity medications contribute to individuals discontinuing the medication (2,59). Therefore, health care professionals should advise individuals of the adverse effects associated with each obesity medication and discuss strategies to

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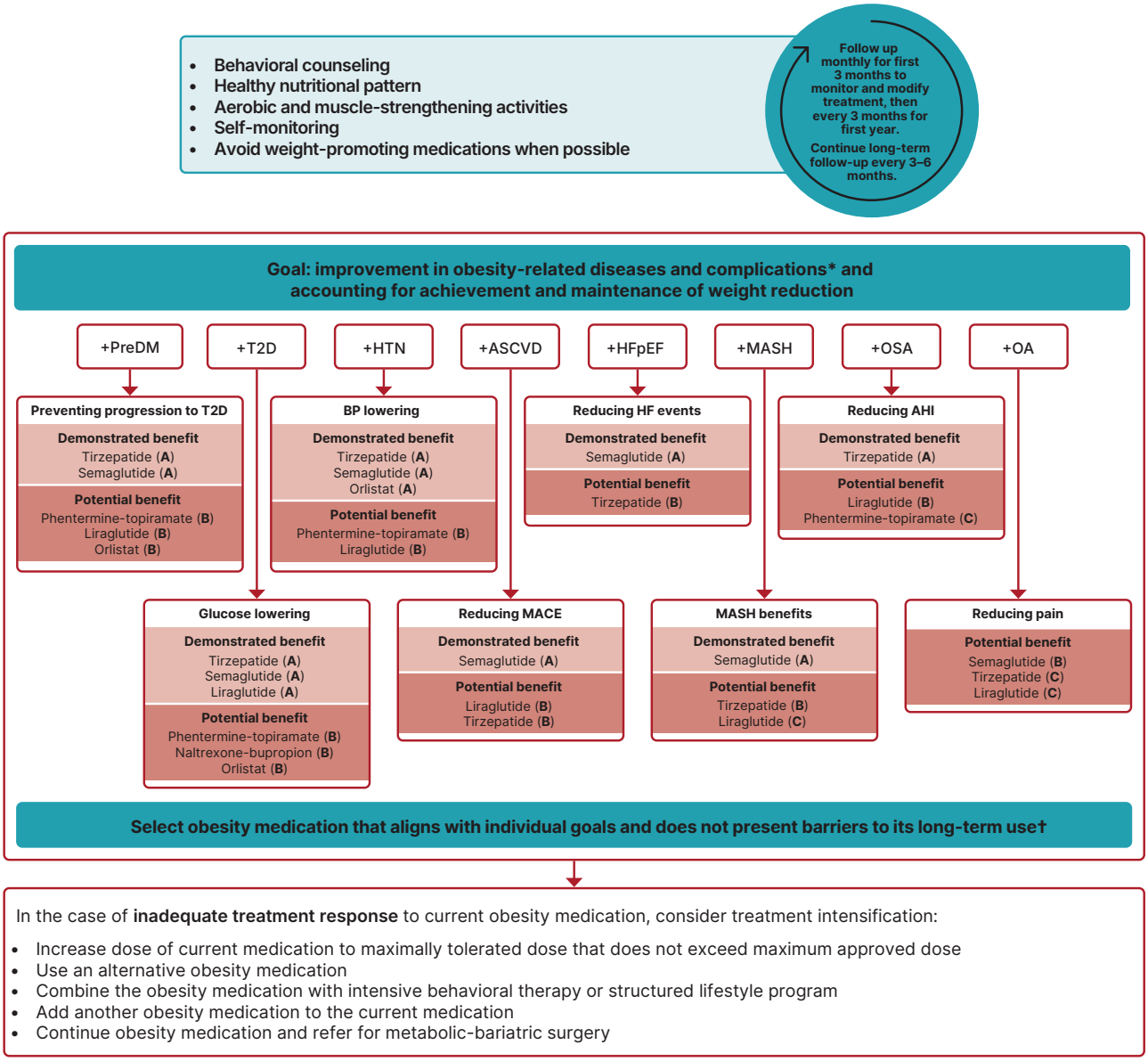

FIGURE 2.2 Obesity medications among adults with obesity-related diseases and complications. Among adults with obesity-related diseases or complications, obesity medications are indicated in adults with overweight or obesity. *Obesity medications are identified as "demonstrated benefit" if there is A-level evidence of benefit in the specified outcome for each obesity-related disease or complication. Obesity medications with B- or C-level evidence for these outcomes are identified as having "potential benefit." Obesity medications are listed in relative order of benefit where medications with greatest benefit are listed first; to date, no head-to-head trials have compared these outcomes in obesity medications. The level of evidence ratings are identified in parentheses. †Barriers to long-term use may include adverse medication effects, insurance coverage, out-of-pocket costs, etc. AHI, apnea hypopnea index; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction–associated steatohepatitis; OA, osteoarthritis; OSA, obstructive sleep apnea; PreDM, prediabetes; T2D, type 2 diabetes.

minimize or manage these effects (Table 2.1). For example, glucagon-like peptide 1 receptor agonists (GLP-1RAs) and a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist (dual GIP/GLP-1RA) are associated with gastrointestinal adverse effects including nausea, diarrhea, constipation, and dyspepsia (60–62), which may be managed by decreasing portion sizes, decreasing intake of high-fat foods, increasing intake of high-fiber foods, avoiding long intervals between meals, and eating the last meal ≥2 h before bedtime (63,64).

For an individual with obesity who does not have any obesity-related diseases or complications, the primary treatment goal is to prevent the development of these

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conditions (Fig. 2.1). Health care professionals should perform a comprehensive medical evaluation before selecting a medication to ensure safety and efficacy. Pharmacotherapy is an important tool for managing obesity, particularly when lifestyle interventions alone are insufficient to achieve and sustain weight reduction (53). The amount of weight reduction necessary to prevent obesity-related diseases and complications varies from person to person, and the health care professional should consider cost, access, tolerability, and individual preferences in the decision-making. Current costs of each obesity medication are summarized in Table 2.4.

Prediabetes

In individuals with obesity, weight reduction is highly effective in preventing or delaying progression to type 2 diabetes (T2D), particularly in high-risk people with prediabetes or metabolic syndrome. T2D prevention is dependent on weight-reduction magnitude, as evident from the Diabetes Prevention Program that demonstrated near-maximal T2D prevention was observed at ∼10% weight reduction with lifestyle intervention (65). Figure 2.2 and Table 2.5 summarize outcomes of obesity medications among individuals with prediabetes. For example, an RCT employing phentermine-topiramate achieved 10% weight reduction and reduced incident T2D by 79% (66), which is a relatively similar T2D reduction to that achieved with metabolic-bariatric surgery (67,68). Orlistat also reduces incident T2D by 37% (69).

More recent studies with GLP-1RA obesity medications are consistent with a weight-reduction goal of ∼10% to prevent T2D progression. An RCT of liraglutide 3 mg produced 6.1% weight reduction and reduced T2D progression by 79% (70). Semaglutide 2.4 mg was highly effective in converting prediabetes to normoglycemia (71), and 9.7% weight reduction with semaglutide was associated with 73% reduction in risk of developing T2D compared with placebo over ∼4 years of observation in the SELECT RCT (72). Tirzepatide 15 mg led to a 93% T2D reduction associated with 19.7% weight reduction in the 3-year SURMOUNT-1 extension study (73); this T2D prevention benefit may reflect incretin effects of the GLP-1 component and GIP bioeffects in addition to weight reduction (74,75).

Type 2 Diabetes

While the relationship between obesity and pathogenesis of T2D is complex, weight reduction represents highly effective therapy for both glycemic management and amelioration of obesity-related diseases and complications. The value of weight reduction as a primary treatment approach in T2D, whether at initial diagnosis or in conjunction with glucose-lowering therapy at any time over the disease course, is emphasized in the ADA's "Standards of Care in Diabetes" (76). Health care professionals should be aware that people with T2D typically lose less weight than individuals without this diagnosis (77). All obesity medications FDA-approved for long-term treatment have been studied in RCTs that enrolled people with T2D (Fig. 2.2 and Table 2.5) (2,78–83). Weight reduction with obesity medication consistently lowers A1C and reduces the need for diabetes medications when compared with lifestyle alone (78–84). With obesity medications, individuals with T2D and obesity also experience blood pressure reductions, improvements in lipids, decreased hepatic transaminases, and improvements in cardiovascular risk biomarkers. Three medications approved for obesity (i.e., liraglutide, semaglutide, and tirzepatide) also have an indication for glycemic management (84–86), although maximum approved doses for T2D are lower for liraglutide and semaglutide than approved doses for obesity.

Given their weight reduction and glucose-lowering benefits, health care professionals should strongly consider a GLP-1RA or dual GIP/GLP-1RA obesity medication as part of the treatment plan in people with obesity and T2D. In the SURMOUNT-2 RCT involving people with T2D and obesity, tirzepatide 15 mg produced weight reduction of 14.7% and resulted in a 2.1% A1C reduction, with nearly half of people achieving normal A1C values (<5.7%) (78). In the STEP 2 RCT, semaglutide 2.4 mg resulted in a 9.6% weight reduction and A1C lowering of 1.6% (79). The SCALE Diabetes trial in people with obesity and T2D demonstrated that liraglutide 3 mg produced a 6.0% weight reduction and 1.3% A1C reduction (80). Severe hypoglycemic episodes were uncommon in individuals randomized to tirzepatide, semaglutide, and liraglutide in these trials (78–80).

If a GLP-1RA or dual GIP/GLP-1RA obesity medication cannot be used, then other obesity medications may be considered. In people with T2D and obesity, phentermine-topiramate 15/92 mg resulted in 9.4% weight reduction and A1C lowering of 1.6% (81). Naltrexone-bupropion 32/360 mg led to a 5% weight reduction in people with obesity and T2D and A1C lowering of 0.6% (82). Orlistat resulted in 6.2% weight reduction and 0.3% A1C decrease in this population (83).

Hypertension

Hypertension is an obesity-related disease (87,88), and one of the benefits of weight reduction is lowering blood pressure. Greater weight reduction leads to greater improvements in systolic and diastolic blood pressure with intensive lifestyle intervention (45). Blood pressure lowering in individuals with and without hypertension is observed with most obesity medications (Fig. 2.2 and Table 2.5) (18,41,42,89–94). For example, tirzepatide 15 mg reduced systolic and diastolic blood pressure by 7.2 mmHg and 4.8 mmHg, respectively (18), and a substudy using 24-h ambulatory monitoring found that tirzepatide substantially reduced daytime and nighttime blood pressures in individuals with elevated baseline systolic pressure (95). It should

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TABLE 2.3 Mechanisms of action and dosing of obesity medications for adults

Medication (route)	Mechanisms of action	Available doses	Manufacturer-recommended dose-escalation schedule*	Maximum approved dose	Dose adjustment in renal impairment†	Impact on oral contraceptive efficacy
Orlistat (oral)	Intestinal lipase inhibitor	120 mg 60 mg (OTC)	None	120 mg TID	Not required	None
Phentermine (oral)	Sympathomimetic amine	8 mg 15 mg 30 mg 37.5 mg	None	8 mg TID 37.5 mg daily	eGFR 15–29 mL/min: 15 mg daily max	None
Phentermine-topiramate (oral)	Sympathomimetic amine combined with GABA augmentation	3.75/23 mg 7.5/46 mg 11.25/69 mg 15/92 mg	Week 1–2: 3.75/23 mg daily Week 3–13: 7.5/46 mg daily Week 14–15: 11.25/69 mg daily‡ Week 16+: 15/92 mg daily	15/92 mg daily	CrCl <50: 7.5/46 mg daily max	Altered bioavailability to OCP components that may cause irregular bleeding
Naltrexone-bupropion (oral)	POMC neuron stimulation via dopamine/norepinephrine reuptake inhibitor and opioid receptor antagonist	8/90 mg	Week 1: 1 tablet daily Week 2: 1 tablet BID Week 3: 2 tablets QAM and 1 tablet QPM Week 4+: 2 tablets BID	16/180 mg BID	Moderate to severe renal impairment: 8/90 mg twice daily max	None
Liraglutide (SQ)	GLP-1 receptor agonist	18 mg/3 mL pen	Week 1: 0.6 mg SQ daily Week 2: 1.2 mg SQ daily Week 3: 1.8 mg SQ daily Week 4: 2.4 mg SQ daily Week 5+: 3.0 mg SQ daily	3.0 mg daily	Not required	None‖
Semaglutide (SQ)	GLP-1 receptor agonist	0.25 mg/0.5 mL pen 0.5 mg/0.5 mL pen 1 mg/0.5 mL pen 1.7 mg/0.75 mL pen 2.4 mg/0.75 mL pen	Week 1–4: 0.25 mg SQ weekly Week 5–8: 0.5 mg SQ weekly Week 9–12: 1 mg SQ weekly Week 13–16: 1.7 mg SQ weekly§ Week 17+: 2.4 mg SQ weekly	2.4 mg weekly	Not required	None‖
Tirzepatide (SQ)	Dual GIP and GLP-1 receptor agonist	2.5 mg/0.5 mL pen or vial 5 mg/0.5 mL pen or vial 7.5 mg/0.5 mL pen or vial 10 mg/0.5 mL pen or vial 12.5 mg/0.5 mL pen or vial 15 mg/0.5 mL pen or vial	Week 1–4: 2.5 mg SQ weekly Week 5–8: 5 mg SQ weekly§ Week 9–12: 7.5 mg SQ weekly Week 13–16: 10 mg SQ weekly§ Week 17–20: 12.5 mg SQ weekly Week 21+: 15 mg SQ weekly	15 mg weekly	Not required	Significant interaction with OCPs¶

BID, twice a day; CrCl, creatinine clearance; eGFR, estimate glomerular filtration rate; GABA, γ-aminobutyric acid; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; OCP, oral contraceptive pill; OTC, over the counter; POMC, proopiomelanocortin; QAM, every morning; QPM, every evening; SQ, subcutaneous; TID, three times a day. *In clinical practice, dose escalation or de-escalation should be tailored to individual treatment response balancing benefits and adverse effects. Information provided is based on manufacturer-suggested dose-escalation schedule; dose-escalation schedule and maintenance dose is often modified based on individual response and goals. †Information is adapted from manufacturer-suggested renal dose adjustment. For individuals with severe renal impairment (eGFR <30 mL/min) or end-stage kidney disease, caution and close monitoring should occur if orlistat, liraglutide, semaglutide, or tirzepatide is used. Phentermine, phentermine-topiramate, and naltrexone-bupropion should be avoided in these individuals. ‡For individuals who achieve ≥3% weight reduction at week 14, phentermine-topiramate may be continued at 7.5/46 mg daily dose. §Indicated doses may also be maintenance doses per manufacturer guidelines. ‖No effect was found on bioavailability of OCP; however, concern has been raised about how delayed gastric emptying from the medication may affect efficacy of OCPs. ¶Advise individuals using oral hormonal contraceptives to switch to a nonoral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation with tirzepatide and for 4 weeks after each dose escalation.

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TABLE 2.4 Median monthly AWP and NADAC of maximum dose of obesity medications*

Medication	Maximum approved dose	Median AWP for 30-day supply† (range)	Median NADAC for 30-day supply† (range)
Orlistat‡	120 mg TID	$651 ($520–$781)	$518 ($416–$619)
Phentermine	37.5 mg daily	$43 ($3–$56)	$2 ($2–$3)
Phentermine-topiramate	15/92 mg daily	$251	NA
Naltrexone-bupropion	16/180 mg BID	$750	NA
Liraglutide	3 mg daily	$1,619	$1,304
Semaglutide	2.4 mg weekly	$1,619	$1,304
Tirzepatide	15 mg weekly	$1,304§	$1,052§

AWP, average wholesale price; BID, twice daily; NA, data not available; NADAC, National Average Drug Acquisition Cost; TID, three times daily. *The costs listed in this table are representative of costs at a national level. These costs may not be representative of an individual's cost and do not account for medication coverage, available discounts from manufacturers, or direct-to-consumer pricing. AWP (252) and NADAC (253) prices are for 30-day supply of maximum or maintenance dose as of 2 July 2025. †Price ranges provided when multiple products (e.g., one or more generic products in addition to the branded product) are commercially available. ‡Orlistat is also available over the counter with maximum approved dose of 60 mg TID. Mean AWP for a 30-day supply is $58 (range $41–$90), and median NADAC is unavailable. §Price data listed is for tirzepatide pens only.

be noted that tirzepatide, semaglutide, liraglutide, and phentermine-topiramate, on average, cause small increases in resting heart rate (~2–4 bpm), although some individuals may experience larger increases (~10–20 bpm). This heart rate change is not clinically detrimental to most individuals, as the rate-pressure product (heart rate × systolic blood pressure) (96–98), which indicates workload on the heart, remains favorable due to blood pressure reductions. Health care professionals should be aware that naltrexone-bupropion does not reduce blood pressure commensurate with weight reduction (89), and both naltrexone-bupropion and phentermine are contraindicated in individuals with uncontrolled hypertension.

Atherosclerotic Cardiovascular Disease

Obesity contributes to atherosclerotic cardiovascular disease (ASCVD) development through multiple mechanisms (99), and the duration of obesity and visceral adiposity are strong predictors of coronary artery disease in epidemiologic studies (100). The magnitude of weight reduction achieved may be particularly critical for ASCVD (99), as modest weight reduction with intensive lifestyle intervention did not reduce the rate of cardiovascular events in adults with T2D and obesity (101); a post hoc analysis of this RCT found that only participants who achieved ≥10% weight reduction had significant reductions in cardiovascular events (102). In adults with obesity and established ASCVD, the treatment plan should include a GLP-1RA with demonstrated benefits or dual GIP/GLP-1RA with potential benefits in reducing cardiovascular events as well as weight reduction (Fig. 2.2 and Table 2.5).

Semaglutide reduces cardiovascular events among high-risk individuals (e.g., those with prior ASCVD or T2D) (103). In the SELECT RCT, semaglutide 2.4 mg resulted in a 20% reduction in adverse cardiovascular outcomes (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in adults with BMI ≥27 kg/m^2 and established cardiovascular disease without diabetes (4). Further, semaglutide produced durable weight reduction (104) and significantly reduced new-onset diabetes and a composite kidney outcome (driven by reductions in new-onset macroalbuminuria) (105). While a cardiovascular outcomes trial evaluating liraglutide 3.0 mg has not been performed, liraglutide 1.8 mg (T2D-approved dose) reduces cardiovascular events in people with T2D at increased cardiovascular risk, including among participants with obesity (5). Similar findings were observed with liraglutide 3.0 mg versus pooled comparators in the SCALE trials (HR 0.42; 95% CI 0.17–1.08) (106), but this analysis was underpowered due to low event rates.

A cardiovascular outcomes trial of dual GIP/GLP-1RA obesity medication has not yet been published; however, there is evidence to support potential ASCVD benefits. Tirzepatide has been shown to significantly improve cardiovascular risk factors (e.g., blood pressure, cholesterol, systemic inflammation, and glycemic management) in people with obesity (18,107). In a SURMOUNT-1 trial post hoc analysis, tirzepatide significantly reduced the predicted 10-year risk of ASCVD events compared with placebo (108). Moreover, in a prespecified participant-level pooled analysis of the SURPASS program, tirzepatide did not increase the risk of major adverse cardiovascular events in people with T2D versus pooled comparators (HR 0.80; 95% CI 0.57–1.11) (109).

The LIGHT trial, which randomized people with BMI 27–50 kg/m^2 at increased cardiovascular risk to naltrexone-bupropion, was designed to evaluate cardiovascular outcomes. In the primary analysis (conducted after 50% of planned events), naltrexone-bupropion did not reduce major adverse cardiovascular events compared with placebo (110). However, due to unplanned early termination after public release of confidential interim data, the LIGHT trial was unable to rigorously establish the safety and efficacy of naltrexone-bupropion compared with placebo. Moreover, most participants permanently

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TABLE 2.5 Summary of key evidence to inform obesity medication selection, by populations with specific obesity-related diseases and complications*

Obesity medication	Mean weight change with obesity medication* (time point)	Select outcomes relevant to population
Adults with obesity and prediabetes: progression to type 2 diabetes (Recommendation 2.7)		
Tirzepatide	−12.3% to −19.7% (176 weeks)	• 1.3% TZP vs. 13.3% PBO received a diagnosis of T2D at 176 weeks (HR 0.07; 95% CI 0.0–0.1; *P* <0.001) (73)
Semaglutide	−13.9% (52 weeks)	• 1% SEMA vs. 3% PBO progressed to T2D at 52 weeks (71) • 1.5% SEMA vs. 6.9% PBO progressed to T2D at 156 weeks (*P* <0.0001) (72)
Phentermine-topiramate	−10.9% to −12.1% (108 weeks)	• Annualized incidence rates for progression to T2D: 1.3% in PHEN-TOP 15 mg/92 mg, 1.8% in PHEN-TOP 7.5 mg/46 mg, and 6.1% in PBO at 108 weeks (66)
Liraglutide	−6.1% (160 weeks)	• 2% LIRA vs. 6% PBO were diagnosed with T2D at 160 weeks (HR 0.21; 95% CI 0.13–0.34; *P* <0.0001) (70)
Orlistat	−5.3% (208 weeks)	• Cumulative incidence of T2D was 6.2% ORL vs. 9.0% PBO at 208 weeks (HR 0.63; 95% CI 0.46–0.86) (69)
Adults with obesity and type 2 diabetes: glucose-lowering efficacy (Recommendation 2.8)		
Tirzepatide	−7.9% to −11.0% (40 weeks) −12.8% to −14.7% (72 weeks)	Mean A1C change • −1.9% to −2.1% TZP vs. +0.0% PBO at 40 weeks (84) • −2.1% TZP vs.−0.5% PBO at 72 weeks (78) Achieved A1C <7% • 87% to 92% TZP vs. 19% with PBO at 40 weeks (84) • Over 80% TZP vs. 36% PBO at 72 weeks (78)
Semaglutide	−4.2% to −4.7% (30 weeks) −7.0% to −9.6% (68 weeks)	Mean A1C change • −1.5% to −1.6% SEMA vs.−0.0% PBO at 30 weeks (85) • −1.5% to −1.6% SEMA vs.−0.4% PBO at 68 weeks (79) Achieved A1C <7% • 72% to 74% SEMA vs. 25% PBO at 40 weeks (85) • 72.3% to 78.5% SEMA vs. 26.5% PBO at 68 weeks (79)
Liraglutide	−4.7% to −6.0% (56 weeks)	Mean A1C change • −0.7% to −1.0% LIRA vs. +0.1% PBO at 26 weeks (254) • −1.1% to −1.3% LIRA −0.3% PBO at 56 weeks (*P* < 0.001) (80) Achieved A1C <7% • 66.7% to 69.2% LIRA vs. 27.2% PBO at 56 weeks (*P* < 0.001) (80)
Phentermine-topiramate	−9.4% (56 weeks)	Mean A1C change • −1.6% PHEN-TOP vs.−1.2% PBO at 56 weeks (*P* = 0.0381) (81) Achieved A1C <7% • 51% to 63% PHEN-TOP vs. 39% to 40% PBO at 56 weeks (81)
Naltrexone-bupropion	−5.0% (56 weeks)	Mean A1C change • −0.6% NB vs.−0.1% PBO at 56 weeks (82) Achieved A1C <7% • 44.1% NB vs. 26.3% PBO at 56 weeks (82)
Orlistat	−6.2% (52 weeks)	Mean A1C change • −0.3% ORL vs. +0.2% PBO at 52 weeks (83)
Adults with hypertension: blood pressure reduction (Recommendation 2.9)		
Tirzepatide	−15.0% to −20.9% (72 weeks)	Mean SBP change • −7.2 mmHg TZP and −1.0 mmHg PBO at 72 weeks (18) • PBO-adjusted ABPM change of −7.4 mmHg for TZP 5 mg, −10.6 mmHg for TZP 10 mg, and −8.0 mmHg for TZP 15 mg on ABPM at 36 weeks (95) Mean DBP change • −4.8 mmHg TZP and −0.8 mmHg PBO groups at 72 weeks (18)
Semaglutide	−14.9% (68 weeks)	Mean SBP change • −6.2 mmHg SEMA and −1.1 mmHg PBO at 68 weeks (*P* <0.001) (42) Mean DBP change • −2.8 mmHg SEMA and −0.4 mmHg PBO at 68 weeks (42)

Continued on p. 14 »

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TABLE 2.5 Summary of key evidence to inform obesity medication selection, by populations with specific obesity-related diseases and complications* (Continued)

Obesity medication	Mean weight change with obesity medication* (time point)	Select outcomes relevant to population
Orlistat	−5.3% (208 weeks)	Mean SBP change • −7.3 mmHg ORL vs.−5.2 mmHg PBO at 52 weeks ($P < 0.01$); −4.9 mmHg ORL vs. −3.4 mmHg PBO at 208 weeks ($P < 0.01$) (69) Mean DBP change • −3.6 mmHg ORL vs.−2.6 mmHg PBO at 52 weeks ($P < 0.01$); −2.6 mmHg ORL vs. −1.9 mmHg PBO at 208 weeks ($P < 0.01$) (69)
Phentermine- topiramate	−7.8% to −9.89% (56 weeks)	Mean SBP change • −5.6 mmHg PHEN-TOP 15/92 mg vs.−2.4 mmHg PBO at 56 weeks ($P < 0.001$) (40) Mean DBP change • 3.8 mmHg PHEN-TOP 15/92 mg vs.−2.7 mmHg PBO at 56 weeks ($P = 0.003$) (40)
Liraglutide	−8.0% (56 weeks)	Mean SBP change • −4.2 mmHg LIRA and −1.5 mmHg PBO at 56 weeks ($P < 0.001$) (41) Mean DBP change • −2.6 mmHg LIRA and −1.9 mmHg PBO groups at 56 weeks ($P < 0.001$) (41)
Adults with obesity and established atherosclerotic cardiovascular disease: reduce cardiovascular events (Recommendation 2.10)		
Semaglutide	−9.4% (104 weeks)	• MACE HR 0.80 (95% CI 0.72–0.90; $P < 0.001$) SEMA vs. PBO over a mean follow-up of 40 months (4)
Liraglutide	−5.7% to −9.2% (≥32 weeks)	• MACE HR 0.42 (95% CI 0.17–1.08) LIRA vs. comparators ≥32 weeks (106) • MACE HR 0.87 (95% CI 0.78–0.97; $P < 0.001$) for liraglutide vs. PBO over a median follow-up of 3.8 years (5)
Tirzepatide	−11.9% to −17.8% (72 weeks)	• Change in 10-year ASCVD risk score −23.5% to −16.4% TZP vs. +12.7% PBO at 72 weeks ($P < 0.001$) (108)
Adults with obesity and heart failure with preserved ejection fraction: reduce heart failure symptoms or events (Recommendation 2.11)		
Semaglutide	−9.8% to −13.3% (52 weeks)	Heart failure symptoms • Mean KCCQ-CSS change 16.6 SEMA vs. 8.7 PBO at 52 weeks ($P < 0.001$) (47) • Mean KCCQ-CSS change 13.7 SEMA vs. 6.4 PBO at 52 weeks ($P < 0.001$) (255) • Mean KCCQ-CSS change 15.0 SEMA vs. 7.5 PBO at 52 weeks ($P < 0.0001$) (118) Heart failure events • SELECT trial ○ Composite HF outcome HR 0.82 (95% CI 0.71–0.96) SEMA vs. PBO over mean follow-up of 40 months (4) • Pooled analysis (SELECT, FLOW, STEP-HFpEF, STEP-HFpEF DM) ○ CV death or HF event HR 0.69 (95% CI 0.53–0.89; $P = 0.0045$) SEMA vs. PBO at ≥52 weeks (121) ○ Worsening HF event HR 0.59 (95% CI 0.41–0.82; $P = 0.0019$) SEMA vs. PBO at ≥52 weeks (121)
Tirzepatide	−13.9% (52 weeks)	Heart failure symptoms • Mean KCCQ-CSS change 19.5 TZP vs. 12.7 PBO at 52 weeks ($P < 0.001$) (48) • Between-group median KCCQ-CSS difference 6.9 favoring TZP over PBO at 52 weeks ($P < 0.001$) (123) Heart failure events • CV death or worsening HF event (HF hospitalization, intravenous drugs in an urgent care setting, or intensification of oral diuretic therapy) HR 0.62 (95% CI 0.41–0.95; $P = 0.026$) TZP vs. PBO over a median follow up of 104 weeks (48)

Continued on p. 15 »

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TABLE 2.5 Summary of key evidence to inform obesity medication selection, by populations with specific obesity-related diseases and complications* (Continued)

Obesity medication	Mean weight change with obesity medication* (time point)	Select outcomes relevant to population
Adults with obesity and metabolic dysfunction-associated steatohepatitis: benefits for MASH (Recommendation 2.12)		
Semaglutide	−8.8% (48 weeks) −10.5% (72 weeks)	• 62.9% SEMA met criteria for steatohepatitis resolution without worsening of fibrosis vs. 34.3% PBO at 72 weeks (95% CI 21.1–36.2; $P < 0.001$) (7) • 36.8% SEMA met criteria for fibrosis resolution without worsening of steatohepatitis vs. 22.4% PBO at 72 weeks (95% CI 7.5–21.3; $P < 0.001$) (7) • 11% (5/47) SEMA had improvement in ≥1 stage of fibrosis without worsening of MASH vs. 29% (7/24) with PBO at 48 weeks (129)
Tirzepatide	−10.7% to −15.6% (52 weeks)	• 44% to 62% of TZP met criteria for resolution of MASH without worsening of fibrosis vs. 10% PBO at 52 weeks ($P < 0.001$) (46)
Liraglutide	−5.5% (48 weeks)	• 39% LIRA met criteria for MASH resolution vs. 9% PBO at 48 weeks ($P = 0.019$) (131) • 9% LIRA had progression of fibrosis vs. 36% PBO at 48 weeks ($P = 0.04$) (131)
Adults with obesity and obstructive sleep apnea: benefits for sleep apnea (Recommendation 2.13)		
Tirzepatide	−17.7% to −19.6% (52 weeks)	• Mean AHI change −25.3 events/h TZP vs. −5.3 events/h with PBO at 52 weeks among participants not using PAP ($P < 0.001$) (6) • Mean AHI change −29.3 events/h TZP vs. −5.5 events/h with PBO at 52 weeks among participants using PAP ($P < 0.001$) (6)
Liraglutide	−5.7% (32 weeks)	• Mean AHI change of −12.2 events/h with LIRA vs. −6.1 events/h with PBO at 32 weeks ($P = 0.0150$) (140)
Phentermine- topiramate	−10.3% (28 weeks)	• Mean AHI change of −31.5 events/h with PHEN-TOP vs. −16.6 events/h with PBO at 28 weeks ($P = 0.0084$) (139)
Adults with obesity and osteoarthritis: benefits for osteoarthritis symptoms (Recommendation 2.14)		
Semaglutide	−13.7% (68 weeks)	• Mean change −41.7 points on WOMAC pain score with SEMA vs. −27.5 points with PBO at 68 weeks ($P < 0.001$) (49)
Liraglutide	−6.6% (52 weeks)	• No differences in daily physical activity time assessed via accelerometer between LIRA and PBO at 52 weeks after achieving ≥5% weight loss and knee pain reduction with 8-week very-low-calorie meal plan before randomization (147) • No difference in KOOS pain score between LIRA and PBO at 52 weeks (256); significant between-group difference in KOOS function subscale (3.8 points; 95% CI 0.9–6.7; $P = 0.01$) (147)
Tirzepatide	Not reported	• In a retrospective cohort, TZP was associated with a significantly lower risk of new osteoarthritis diagnosis compared with SEMA (HR 0.57; 95% CI 0.50–0.65; $P < 0.0001$) (148)

A1C, hemoglobin A1c; ABPM, ambulatory blood pressure monitoring; AHI, apnea-hypopnea index; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; KOOS, Knee injury and Osteoarthritis Outcome Score; LIRA, liraglutide; MACE, major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke); MASH, metabolic dysfunction–associated steatohepatitis; NB, naltrexone-bupropion; ORL, orlistat; PAP, positive airway pressure; PBO, placebo; PHEN-TOP, phentermine-topiramate; SBP, systolic blood pressure; SEMA, semaglutide; T2D, type 2 diabetes; TZP, tirzepatide; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. *Of note, phentermine is not included in this table, as all outcomes reported require long-term trials and phentermine has only been studied in short-term RCTs (28 weeks or less) to date.

discontinued study medication by 1-year post-randomization. There are no cardiovascular outcomes trials for orlistat, phentermine, or phentermine-topiramate.

Heart Failure With Preserved Ejection Fraction

Obesity is a leading driver of heart failure with preserved ejection fraction (HFpEF) onset and progression (111–115), and individuals with obesity and HFpEF display unique clinicopathological features (e.g., increased plasma volume and greater cardiac remodeling) when compared with individuals with HFpEF without obesity (116). Modest weight reduction among individuals with obesity and HFpEF through lifestyle change improves aerobic capacity, New York Heart Association functional class, and quality of life (117). In adults with obesity and HFpEF, the treatment plan should include a GLP-1RA or dual GIP/GLP-1RA with demonstrated improvements in heart failure (HF)-related symptoms or events (Fig. 2.2 and Table 2.5).

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In the STEP-HFpEF RCT, semaglutide 2.4 mg significantly improved HF-related symptoms and functional limitations and reduced body weight (11% placebo-subtracted reduction) in people with BMI ≥30 kg/m^2 and chronic symptomatic HF with left ventricular ejection fraction (LVEF) ≥45% (46). In pooled analyses, semaglutide improved exercise function and natriuretic peptide levels (118), reduced diuretic requirements (119), and attenuated adverse myocardial remodeling (120). In a prespecified pooled analysis of the STEP-HFpEF Program, SELECT, and FLOW trials, semaglutide reduced cardiovascular death or HF events by 31% compared with placebo in participants with HF and LVEF ≥40% (121).

Tirzepatide has also been shown to reduce HF events in people with obesity and stable chronic HFpEF. Among individuals with BMI ≥30 kg/m^2 and HF with LVEF ≥50% enrolled in the SUMMIT RCT, tirzepatide improved HF-related health status and reduced the rate of cardiovascular death or a worsening HF event by 38% (48), although number of events was relatively low (36 with tirzepatide and 56 with placebo). Additional benefits on body weight (12% placebo-controlled reduction), exercise function, left ventricular mass, and paracardiac adipose tissue were also observed (122,123).

Metabolic Dysfunction–Associated Steatohepatitis

Metabolic dysfunction–associated steatohepatitis (MASH) is defined as the presence of steatohepatitis and no alcohol consumption or consumption in amounts unlikely to directly cause adverse liver outcomes (alcohol intake <20 g/day for women and <30 g/day for men) (124). Fibrosis is a predictor of disease progression (125) and is strongly linked to liver-related outcomes and death (126). Histologically, fibrosis is staged based on severity and distribution of scar tissue. Clinically significant fibrosis is defined as stage ≥F2 (moderate; sinusoidal and portal fibrosis), advanced fibrosis is F3 (i.e., bridging fibrosis, usually central-to-portal or central-to-central bridges), and F4 is cirrhosis (124). Among people with MASH, weight reduction of ≥10% may be needed to reverse steatohepatitis and improve fibrosis (127). In adults with obesity and MASH with moderate or advanced fibrosis, a GLP-1RA or dual GIP/GLP-1RA is preferred for obesity treatment because of the benefits or potential benefits on MASH (Fig. 2.2 and Table 2.5). While not specifically tested among individuals with MASH, health care professionals should be aware that the dose of naltrexone-bupropion needs to be adjusted in the setting of moderate hepatic impairment.

In a planned interim analysis of the ESSENCE RCT, semaglutide 2.4 mg significantly improved liver histology compared with placebo in individuals with biopsy-defined MASH and fibrosis stage F2 or F3 (7). Mean BMI was 34.3 kg/m^2 and 35.0 kg/m^2 in the semaglutide and placebo groups, respectively. Resolution of steatohepatitis with no worsening of liver fibrosis occurred in 62.9% of semaglutide participants and 34.3% of placebo; a reduction in liver fibrosis with no worsening of steatohepatitis was reported in 36.8% of semaglutide participants and 22.4% of placebo. Mean weight reduction with semaglutide was 10.5%. Prior phase 2 RCTs of semaglutide among individuals with MASH demonstrated significantly increased likelihood of MASH resolution (128) and improved cardiometabolic parameters (129). A meta-analysis (8 RCTs) demonstrated the short-term efficacy and safety of semaglutide in reducing liver fat content and improving liver stiffness compared with placebo (130). Less evidence exists regarding the use of liraglutide in MASH. In a phase 2 RCT of individuals with BMI ≥25 kg/m^2 and biopsy-confirmed MASH, liraglutide 1.8 mg demonstrated histological resolution of MASH and slowed fibrosis progression compared with placebo (131). Pilot studies comparing liraglutide 3 mg and structured lifestyle interventions found no significant difference in liver-related outcomes (132,133).

Tirzepatide has shown promise in treating MASH. In the phase 2 SYNERGY-NASH RCT, individuals with biopsy-confirmed MASH and stage F2 or F3 fibrosis were randomized to tirzepatide or placebo; 62% of the tirzepatide 15 mg group met criteria for resolution of MASH without worsening of fibrosis at 52 weeks compared with 10% in the placebo group (46). Overall, 51% of tirzepatide 15 mg participants improved at least one fibrosis stage without worsening of MASH as compared with 30% of placebo participants. Mean weight reduction was 15.6% with tirzepatide 15 mg. Lower doses of tirzepatide (5 mg and 10 mg) were also tested and showed benefits relative to placebo.

There currently is no direct evidence evaluating outcomes of the use of GLP-1RA or dual GIP/GLP-1RA obesity medications among individuals with obesity and metabolic dysfunction–associated steatotic liver disease (MASLD). These medications may be an effective and safe option for achieving sustained weight reduction in this population, given the demonstrated or potential benefits on MASH.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is an obesity-related disease characterized by partial or complete upper airway obstruction during sleep, leading to sleep fragmentation and hypoxemia (114). The prevalence of moderate-to-severe OSA, defined as AHI ≥15 events/h on polysomnography, increases with increasing body weight (134). OSA is associated with increased mortality in people with obesity (135,136). A 10% body weight reduction is associated with a 26% lower AHI (134). Weight reduction with intensive lifestyle intervention significantly decreases AHI and increases the likelihood of OSA remission (137,138).

Several obesity medications improve OSA in RCTs (Fig. 2.2 and Table 2.5) (6,139,140), and AHI reduction is strongly

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related to the weight-reduction magnitude achieved with the obesity medication (139,140). To date, the greatest magnitude of benefit has been with tirzepatide. In the SURMOUNT-OSA trials, once-weekly tirzepatide (10 or 15 mg) significantly reduced AHI by more than 20 events/h compared with placebo in adults with obesity and moderate-to-severe OSA, among individuals treated with and without positive airway pressure (PAP) (6). Mean weight reduction with tirzepatide was ≥15%. Over 40% of SURMOUNT-OSA participants treated with tirzepatide experienced improvements in OSA severity to below typical thresholds to recommend PAP therapy. In short-term RCTs, phentermine-topiramate and liraglutide 3.0 mg reduced AHI by 15 and 6 events/h, respectively, compared with placebo among people with obesity and moderate-to-severe OSA (139,140). Inclusion of obesity medications may also have added benefits of improved systolic blood pressure, glycemia, and body weight reduction that individuals with OSA may be unlikely to achieve with PAP therapy alone (141,142). In addition to established OSA treatment approaches (e.g., PAP, airway stimulation, and splinting devices), the evidence supports obesity medications as part of the treatment plan for people with obesity and OSA.

Osteoarthritis

Osteoarthritis is an obesity-related disease, particularly knee osteoarthritis (143,144). Weight gains of ≥10% are associated with worsening pain and physical function (145), and weight reduction of similar magnitude may result in symptom improvements (146). In adults with obesity and moderate osteoarthritis, the treatment plan should prioritize a GLP-1RA or dual GIP/GLP-1RA with potential to improve osteoarthritis symptoms (Fig. 2.2 and Table 2.5). In a 68-week trial involving individuals with obesity and moderate knee osteoarthritis, semaglutide 2.4 mg significantly improved knee pain scores and reduced body weight compared with placebo (49); participants also experienced greater improvements in physical function. Less evidence exists regarding the use of liraglutide in osteoarthritis, which may only have modest benefits in physical function (147). A retrospective cohort study found that individuals prescribed semaglutide, liraglutide, or tirzepatide had a reduced risk of osteoarthritis diagnosis (148). Individuals prescribed tirzepatide had a significantly lower risk of osteoarthritis compared with individuals prescribed semaglutide or liraglutide.

Long-term Management of Obesity Medications

Recommendations

2.15 Obesity medications requiring dose escalation should be initiated at a low dose and uptitrated gradually, as needed, based on tolerability **A** and clinical response **E**.

2.16 Continue obesity medications after reaching treatment goals to maintain health benefits, as discontinuation often results in weight recurrence and worsening or reemergence of cardiometabolic risk factors or obesity-related diseases and complications **A**. The individualized maintenance dose should balance efficacy, health benefits, and tolerability and therefore may not necessarily be the maximum approved dose **A**.

2.17 In individuals with an inadequate response to current obesity medication, intensify treatment to improve outcomes. Dose escalation to maximum dose is recommended **A**. If maximum tolerable dose is already used, then consider switching to an alternative obesity medication **C**, adding intensive lifestyle therapy **B**, combining obesity medications **C**, or referring to metabolic-bariatric surgery **A**.

Gradual dose escalation is a critical strategy in obesity pharmacotherapy to optimize efficacy while improving tolerability. Many obesity medications have dose-dependent adverse effects, particularly gastrointestinal symptoms and neuropsychiatric effects (e.g., mood changes), that necessitate a stepwise escalation (39–42). For example, the SURMOUNT-1 RCT demonstrated that a 20-week dose-escalation period was essential to reaching the target therapeutic dose of tirzepatide while maintaining tolerability (18). Tirzepatide dose escalation often occurs more gradually in real-world clinical practice than what occurred in trials (149), reflecting the importance of adjustments based on individual response. Experiencing adverse effects has been significantly associated with obesity medication discontinuation (59). Individuals who experience early intolerance to high doses often benefit from remaining on low doses longer before advancing. Health care professionals may consider this approach to improve tolerability, particularly for older individuals, people with gastrointestinal sensitivities, or individuals with obesity-related diseases or complications.

As obesity is a chronic disease, long-term pharmacotherapy is typically needed after treatment goals are achieved to sustain benefits. Real-world evidence thus far shows that long-term use of obesity medications can maintain ≥10% weight reduction (150). Health care professionals and stakeholders who determine benefits coverage for health insurance should be aware that clinical trials show that discontinuation of obesity medications results in recurrence of most of the weight lost within 1 year and reversal of prior cardiometabolic improvements (107,151–153). Recent research has identified obesity medication costs as a factor contributing to individuals' discontinuing treatment (154). Loss of insurance coverage for obesity medications makes these treatments unaffordable for many individuals and contributes to their feelings of hopelessness, anger, and stigmatization (155). Obesity medications should be continued after reaching treatment and weight reduction goals to maintain health benefits and avoid weight recurrence (107,150,151,153,156).

The long-term maintenance dose of obesity medication should be tailored to optimize health benefits while minimizing adverse effects; multiple clinical trials have employed a "maximum tolerated dose" strategy to improve

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medication-taking behavior (6,49,107). Beneficial outcomes can be achieved with a maintenance dose that is not the maximum dose. For example, a 20% cardiovascular risk reduction was noted in the SELECT trial despite flexible dosing of semaglutide (4). Health care professionals should take a practical approach of balancing risk and benefit to tailor the maintenance dose to each individual, which may include continuing obesity medication on the lowest effective dose (which may not be an FDA-approved maintenance dose), using intermittent therapy, switching to an alternative obesity medication, or stopping medication followed by close monitoring.

Inadequate Treatment Response

The response to all obesity medications is highly heterogeneous between individuals (157–159); therefore, health care professionals should regularly reassess their effectiveness in achieving treatment and weight reduction goals. For individuals with inadequate treatment response (e.g., not reaching intermediate treatment goals in 6 months or maintaining treatment goals), avoid treatment inertia by re-evaluating ongoing therapies and intensifying treatment with additional approaches. Increasing the dose of the current obesity medication to the maximum tolerated dose should be the first step (18,40,79,80). If the initial obesity medication or dose escalation of that medication is not well tolerated by the individual, then the health care professional should consider changing to a different obesity medication and discontinuing the ineffective medication. For individuals on a high-dose obesity medication that is ineffective, health care professionals may consider de-escalating medication dose slowly until reaching discontinuation to improve tolerability. Health care professional monitoring during de-escalation may be particularly important when discontinuing phentermine-topiramate and naltrexone-bupropion. Studies have shown that individuals who have inadequate response to one obesity medication can benefit from switching to another obesity medication (160–164). Beyond these approaches, health care professionals may also consider combining obesity medications, pairing obesity medication with intensive behavioral therapy/structured lifestyle program, or referring to metabolic-bariatric surgery.

Intensive behavioral therapy (IBT) or structured lifestyle programs comprise frequent clinic visits for nutrition, physical activity, and behavior change counseling to treat obesity. Multiple RCTs have demonstrated that combining IBT with obesity medication yields relatively greater weight reduction and health benefits (22,23,165,166). Combining IBT with select obesity medications (e.g., naltrexone-bupropion or liraglutide) is particularly beneficial for achieving greater magnitude of weight reduction relative to that achieved with lifestyle counseling (22,167). Adding IBT to semaglutide may have a diminished benefit relative to lifestyle counseling (24,42), although no trials have directly compared semaglutide with and without IBT. For example, one RCT found that naltrexone-bupropion with lifestyle counseling resulted in 6.1% weight reduction at 1 year (39) as compared with another RCT that found naltrexone-bupropion with IBT resulted in 9.3% weight reduction at 1 year (22). Similarly, an RCT found that tirzepatide with lifestyle counseling resulted in 20.9% weight reduction (18), while another RCT found that combining tirzepatide with IBT resulted in a 24.5% weight reduction (25). These results may suggest that combining obesity medication with IBT may improve outcomes relative to obesity medication with counseling alone. Referral should be considered where there is access to such programs.

For individuals who have a partial treatment response to the current obesity medication, it may be reasonable to combine this medication with another obesity medication. Health care professionals can target different weight-regulating pathways by combining obesity medications; in fact, weight reduction achieved by low-dose combination therapy may exceed that of high-dose monotherapy. For example, an RCT found that weight reduction achieved with phentermine-topiramate 7.5/46 mg was greater than phentermine 15 mg alone (10.4% vs. 7.4%, respectively) (50). Among individuals with T2D, the addition of naltrexone-bupropion to a GLP-1RA resulted in 5.2% greater weight reduction than that for individuals on placebo and GLP-1RA (168). However, a small pilot study found that the addition of phentermine to liraglutide did not produce additional clinically meaningful weight reduction in individuals who had already lost 12.6% of initial weight with liraglutide alone (169). The use of multiple obesity medications for chronic weight management mirrors treatment paradigms established for other chronic diseases, and this approach is also supported by long-term data in retrospective cohorts (150,156). However, there are no RCTs examining how to best escalate therapy for individuals with inadequate treatment response.

Metabolic-bariatric surgery should be offered to eligible individuals with inadequate treatment response to lifestyle modification and pharmacotherapy. Metabolic-bariatric surgery produces substantial weight reduction and achieves multiple health benefits including reduced blood pressure (170), improved glycemia among people with T2D (171), and reduced cardiovascular events (172). In addition, several studies have shown the benefit and safety of adding obesity medication after an individual has undergone metabolic-bariatric surgery (173–175). Therefore, obesity medications may also be added to augment weight reduction and health benefits in individuals who have undergone surgery where a weight plateau occurs before achieving their treatment goals or who are experiencing weight recurrence. Health care professionals should be aware of nonsurgical procedures to treat obesity, and a future section of the "Standards of Care for Overweight and Obesity" will provide recommendations regarding surgical and nonsurgical procedures to treat obesity.

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Lifestyle Intervention With Obesity Medications

Recommendations

2.18 Nutrition recommendations should be tailored to individuals' preferences and nutritional needs **C**. Consider referral to a registered dietitian nutritionist **A**.

2.19 Counsel and regularly monitor individuals using obesity medications to ensure adequate nutritional intake, with particular attention to preventing protein insufficiency and micronutrient deficiencies during the active phase of weight reduction **E**.

2.20 Counsel individuals treated with obesity medications on the need for adequate protein intake **A** and muscle-strengthening activities **A** to minimize muscle loss that occurs with weight reduction.

When making nutrition recommendations, health care professionals should consider an individual's medical history, dietary intake and nutritional status, social determinants of health, personal values, and preferences. A meta-analysis concluded that personalized nutrition interventions are more effective at improving dietary intake than usual care, with mixed improvements in weight and waist circumference (16 studies) (176); however, another meta-analysis found that participant choice in dietary intervention did not confer a weight reduction benefit (9 studies) (177). Given that in-depth nutritional counseling may be challenging in clinical practice (178–180), referral to a registered dietitian nutritionist (RDN) for nutritional guidance should be considered for people prescribed obesity medications. RDNs use medical nutrition therapy—a counseling process that includes nutritional assessment, diagnosis, intervention, and monitoring and typically results in the prevention, delay, or management of disease (181). RDN-delivered obesity interventions improve BMI, waist circumference, blood pressure, and quality of life (182). In a systematic review (26 RCTs), RDN consultations were effective for improving nutritional quality as well as weight reduction and diabetes outcomes in the primary care setting (183). RDNs may also address other important behaviors including physical activity, sleep hygiene, stress management, problem solving, and goal setting (184).

Nutritional counseling is an important element in obesity management and improved health, particularly for people receiving obesity medications. Given the appetite-suppressing effects of many obesity medications, individuals may become vulnerable to inadequate nutrition due to diminished hunger, desire to eat small portions, or skipping meals. Nutritional counseling should prioritize consumption of nutrient-dense foods such as lean proteins, fruits, vegetables, whole grains, and healthy fats. A minimum of 60 g of protein daily should be recommended, although higher protein intake is often advised during weight reduction (1.2–1.6 g/kg per day) (185). An adequate daily intake of water 3.7 L (~13 cups) for men and 2.7 L (~9 cups) for women is also recommended (186). These protein and fluid goals should be modified among individuals with certain conditions, such as chronic kidney disease or heart failure. Eating patterns and nutritional adequacy should be assessed at each visit.

In general, adults with obesity have lower intakes of vitamins A, C, D, and E as well as calcium and magnesium compared with adults without obesity (187). The appetite suppressive effects of obesity medications lead to caloric reduction (188,189), and this reduced food consumption may be insufficient to meet essential micronutrient requirements in some individuals (190,191). Multivitamin mineral supplements may be considered for individuals who consume less than 1,200 kcal/day, exclude micronutrient-rich food groups from their usual intake (e.g., fruits and vegetables, whole grains, proteins, and nuts and seeds), are strict vegetarians, have underlying health conditions that impair nutrient absorption, are older (aged >50 years), or experience excessive weight reduction (192). Multivitamin mineral supplement use has been associated with lower risk of nutrient deficiencies (187,193). A daily multivitamin supplement is also recommended with orlistat therapy due to decreased absorption of fat-soluble vitamins (194). If nutritional intake remains inadequate due to obesity medication effects, the health care professional should consider dose reduction of the obesity medication.

All weight-reduction interventions are associated with reductions in fat mass and lean body mass (LBM), although the proportions of the two components vary over time and are determined by multiple factors (e.g., protein intake, exercise, sex, age, and baseline adiposity). In general, many nutrition intervention studies report that fat mass loss contributes to ~75% of body weight reduction, while LBM contributes to ~25% of body weight reduction (195). A concern over the risk of excessive skeletal muscle loss, a component of LBM, has been raised with the use of obesity medications, particularly medications that result in ≥15% weight reduction. In meta-analyses of GLP-1RA obesity medications, LBM loss accounts for 25% to 30% of total weight reduction (196,197). Similarly, a substudy of participants on tirzepatide found that LBM loss accounts for 25% of total weight reduction (198). Despite lean mass loss, questionnaires consistently demonstrate improvements in physical function and quality of life with weight reduction (199,200). However, older adults with obesity or adults with severe obesity-related diseases or complications may be vulnerable to later onset of sarcopenic obesity—a condition characterized by reduced skeletal muscle mass and function (201)—and lower bone mineral density due to excessive weight reduction. Health care professionals should consider regularly assessing muscle strength and function by one or more office-based techniques (e.g., chair-to-stand, handgrip, knee-extensor strength, and walk test) (201) and using functional instruments (e.g., SARC-F questionnaire) (202).

The treatment plan should emphasize optimizing protein intake through dietary counseling and supplementation (as needed), alongside resistance training to preserve

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lean mass. A meta-analysis (47 RCTs) concluded that a protein intake exceeding 1.3 g/kg/day is beneficial in maintaining muscle mass during weight reduction among adults with obesity (203). However, other studies have found that its benefit on muscle strength is observed only when enhanced protein intake is combined with resistance training (204). A meta-analysis (114 RCTs) concluded that lean mass was maintained in interventions involving resistance training and caloric restriction, providing evidence that resistance-based exercise programs should be considered within multicomponent obesity treatment (205). Health care professionals should assess baseline activity levels and tailor recommendations to individual needs and context. Aerobic activity should also be included in a comprehensive treatment plan, given its cardiometabolic benefits. In a 1-year RCT, the combination of moderate-to-vigorous-intensity aerobic exercise and liraglutide was most beneficial in total body weight and percent fat loss relative to either treatment alone after an initial 8-week low calorie meal plan (21), and this combination also slowed weight recurrence and preserved bone health over an additional 1-year observational period (206,207).

Special Populations and Circumstances

Recommendations

2.21 Obesity medications should not be used during pregnancy, in individuals actively trying to become pregnant, or during lactation **E**.

2.22 Individuals of childbearing potential with obesity being considered for obesity medication should be counseled on contraception options **A** and the impact of some obesity medications on contraception efficacy **C** (Table 2.3).

2.23 Preconception planning should address the time frame for discontinuing obesity medications, and optimal treatment of obesity and related diseases and complications in preparation for pregnancy **E**.

2.24a Use of compounded products that are not approved by the FDA is not recommended due to uncertainty about their content and resulting concerns about safety, quality, and effectiveness **C**.

2.24b If an obesity medication is unavailable (e.g., in shortage), a switch to a different FDA-approved obesity medication is recommended, as clinically appropriate **E**. Upon resolution of the unavailability, reassess the appropriateness of resuming the original FDA-approved obesity medication **E**.

People of Childbearing Potential

All obesity medications are contraindicated in individuals who are pregnant or actively trying to conceive and are not recommended for use in individuals who are breastfeeding. Some obesity medications have been linked with fetal harm (208–210); notably, topiramate use during pregnancy is associated with major congential malformations (e.g., cleft lip/palate) and being small for gestational age in the fetus. Health care professionals should be aware of the FDA risk evaluation and mitigation strategy (REMS) for phentermine-topiramate. It is typically recommended that individuals of childbearing potential considering pregnancy stop obesity medications at least 2 months before a planned pregnancy, and intensification of lifestyle behavioral therapy may be needed to maintain weight.

While taking obesity medications, individuals of childbearing potential should receive counseling regarding the use of reliable methods of contraception (211,212). Health care professionals should be aware that weight reduction may increase fertility (213,214), so discussing a plan for reliable contraception should be performed in all people of childbearing potential. Some obesity medications may affect oral contraceptive medications (OCP) (Table 2.3), and individuals using OCPs should be advised of these risks. Tirzepatide has a clinically significant interaction with OCPs (215); therefore, it is recommended that individuals be advised to switch to a nonoral contraceptive method or add a barrier method of contraception for 4 weeks after tirzepatide initiation and for 4 weeks after each dose escalation (216). While bioavailability of OCPs has not been affected in studies with semaglutide and liraglutide (217,218), the delayed gastric emptying effect of these medications has been raised as a potential concern, although this effect typically diminishes over time. OCP bioavailability decreases with phentermine-topiramate; however, the degree of impact is not typically associated with increased risk of pregnancy with topiramate doses contained in this combination (219). Individuals taking OCPs and phentermine-topiramate may experience irregular bleeding (spotting) more frequently. Individuals should be advised to continue their OCP if spotting occurs and notify their health care professional if it is troubling (220). Bioavailability of OCPs is not affected by naltrexone-bupropion or orlistat (221,222).

Compounded Medications

Compounded medications do not undergo FDA review for safety, effectiveness, and quality before they are marketed (223). Recent studies have raised concerns about compounded obesity medications regarding impurities and adverse effects (224–228). The FDA considers the use of compounded obesity medications as risky, and the ADA discourages use of compounded GLP-1RA and dual GIP/GLP-1RA products due to safety, quality, and effectiveness concerns (229).

Clinical Practice Considerations With Obesity Medications

Recommendations

2.25 Clinical practices that are unable to implement the recommended infrastructure to support the pharmacologic treatment of obesity should consider referring people to

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health care professionals with competency in obesity medicine **C**.

2.26 Health care professionals who prescribe obesity medications should be knowledgeable on their efficacy, indications, contraindications, adverse effects, benefits, and financial costs **C**.

2.27 Health care professionals should complete a comprehensive evaluation for obesity and obesity-related diseases and complications on each person before prescribing an obesity medication **E**.

2.28 Clinical practices should provide behavioral and lifestyle therapy for people prescribed obesity medications **A**. If in-house services are unavailable, refer to and collaborate with structured lifestyle programs, registered dietitian nutritionists, or other qualified health care professionals with expertise in delivering these interventions **A**.

2.29a After initiating an obesity medication, health care professionals should arrange for follow-up with individuals at least monthly during the first 3 months of treatment to support positive medication-taking behavior by assessing efficacy, managing adverse effects, and monitoring health status **B**. Follow-up can be delivered via telehealth or delivered by interprofessional members of the treatment team, such as registered dietitian nutritionists or nurses, to facilitate timely and effective care **C**.

2.29b For the remainder of the first year of obesity medication treatment, individuals should have follow-up visits at least every 3 months with trained health care professionals to continue monitoring efficacy and safety **C**. Thereafter, follow-up visit frequency may be reduced to every 6 months for long-term management **C**.

2.30 Clinical practices should consider allocating resources to manage prior authorizations for obesity medications as a strategy to reduce the likelihood that these requirements alter health care professionals' treatment decisions **E**.

Clinical practices may need to implement changes to support obesity medication prescribing (Recommendations 2.25–2.30) with the aims of ensuring safety, improving tolerability, and promoting medication-taking behavior. For clinical practices unable to make these changes, clinicians should consider referring people with obesity to health care professionals with competency in obesity medicine (230). Studies have found that obesity medicine physicians offer comprehensive obesity care, which includes lifestyle counseling, obesity medications, and perioperative care for metabolic-bariatric surgery (231–233). In a recent study, individuals who received care from an obesity medicine physician were significantly more likely to receive evidence-based obesity treatment and achieve greater weight reduction than matched control individuals (234).

Given that education and training on obesity treatment is lacking or insufficient in many medical schools, residency programs, and fellowships (235), many health care professionals are unfamiliar with obesity medications and have limited experience with their prescribing (236,237). Addressing this knowledge gap is important prior to integrating obesity medications into practice; health care professionals should understand the indications, contraindications, efficacy, benefits, adverse effects, and financial costs for each obesity medication. Studies have found that educating health care professionals on obesity care, including obesity medications, leads to increased self-efficacy in discussing obesity medications (238,239).

Prior to prescribing an obesity medication, health care professionals should complete a comprehensive evaluation that includes eliciting a history relevant to obesity, performing a physical examination, and obtaining laboratory testing to evaluate for obesity-related diseases and complications that may inform selection of obesity medication. Table 2.6 provides a brief overview of select history and physical exam elements that should be obtained. A future section of the "Standards of Care for Overweight and Obesity" will provide recommendations and additional details regarding the diagnosis, evaluation, and staging of obesity. A comprehensive physical examination should be performed to evaluate for causes of obesity (37). Height and weight should be measured, and BMI should be calculated to categorize the class of obesity. Waist circumference should be measured with the proper technique, and waist-to-height ratio should be calculated ($\geq$0.5 indicates central adiposity with increased risk of T2D and cardiovascular disease) (240,241). Blood pressure should be measured with an appropriately sized cuff to minimize measurement error; importantly, blood pressure values are used to inform obesity medication selection (e.g., elevated blood pressure is a contraindication to naltrexone-bupropion and phentermine).

Health care professionals should document whether an individual has a history of the following obesity-related diseases and complications that may inform obesity medication selection: prediabetes, T2D, hypertension, ASCVD, HFpEF, MASH, OSA, or osteoarthritis. If the individual has not been evaluated for these conditions, the health care professional should obtain a history and complete a physical examination pertinent to the condition and obtain additional testing, as appropriate, to establish a diagnosis (Table 2.6). Clinical practices should be prepared to conduct comprehensive initial evaluations and to continue monitoring identified obesity-related diseases and complications over time.

As obesity medications must be used in combination with lifestyle modification, clinical practices should determine their approach to delivering this care, either as a service provided within the practice or in collaboration with health care professionals or services outside the practice. Lifestyle interventions can be delivered within the primary care setting. A systematic review (56 RCTs) showed that primary care–based interventions for adults with obesity were effective in reducing weight and waist circumference (242); the average intervention duration

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TABLE 2.6 Select components of a medical evaluation suggested prior to prescribing obesity medications*

History elements	Physical examination elements	Diagnostic testing elements
Weight history • Weight gain pattern and body weight trajectory • Highest and lowest body weight as an adult • Characteristics at the onset of overweight (e.g., age, life events, contributing factors) • Past or current use of weight-promoting medications • Past and current treatments and responses, including lifestyle, medication, procedures, and surgery • Past and current disordered eating • Personal goals and readiness to change Lifestyle behaviors • Eating patterns • Physical activity • Stress and coping • Sleep • Personal and cultural preferences for nutrition and physical activity Past medical history of obesity-related diseases and complications† • Prediabetes • Type 2 diabetes • Hypertension • Atherosclerotic cardiovascular disease • Heart failure with preserved ejection fraction • Metabolic dysfunction–associated steatohepatitis or metabolic dysfunction–associated steatotic liver disease • Obstructive sleep apnea • Knee osteoarthritis • Others People of childbearing potential • Current contraception strategy • Upcoming plans for pregnancy	Anthropometrics • Weight and height (measured) • Calculate BMI • Waist circumference (measured), as appropriate‡ • Calculate waist-to-height ratio, as appropriate‡ Vital signs • Blood pressure (measured) • Heart rate (measured) Physical examination • Cardiac exam • Pulmonary exam	Laboratory testing • A1C • Electrolytes including Cr and eGFR • AST, ALT, and platelet count to calculate FIB-4 • TSH • Lipid panel • Urine pregnancy test Other testing, as clinically appropriate • Echocardiogram • Vibration-controlled transient elastography • Sleep study • Knee X-ray

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 score; TSH, thyroid-stimulating hormone. *Health care professionals should consider the listed elements as part of a medical evaluation prior to prescribing an obesity medication; however, this list should not be interpreted as required or as the only elements that should be assessed (e.g., family history, social history). †The specific diseases and complications listed identify conditions that may influence selection of obesity medication. If individuals do not have a history of any of these conditions, health care professionals should assess whether an individual has symptoms suggestive of one of these conditions that would warrant further diagnostic testing. ‡Measurement of waist circumference and calculation of waist-to-height ratio may be warranted to identify individuals at elevated risk of morbidity and mortality (257–259).

was approximately 12 months. Another systematic review (12 RCTs) in adults with obesity receiving behavioral treatment through primary care found that interventions prescribing reduced energy intake (e.g., ≥500 kcal/day deficit) and increased physical activity with traditional behavioral therapy were associated with greater weight reduction than interventions without these three specific components (243). In addition, more treatment sessions delivered by trained interventionists (in-person or remote) were associated with greater weight reduction. As appropriate, clinical practices may consider referring individuals with obesity to IBT or structured lifestyle programs in their community. The effectiveness of combining obesity medication with a structured lifestyle program has also been demonstrated with an employer-based weight management program (165) and within the Veterans Health Administration's MOVE! weight management program (166). Clinical practices can also consider delivering IBT within the practice. An RCT evaluated liraglutide 3.0 mg with IBT versus IBT with placebo in adults with obesity in a primary care setting (23); the delivery of IBT within the primary care setting was feasible, and the combination of liraglutide and IBT resulted in significantly greater weight reduction than IBT alone.

Following up with individuals started on obesity medications is recommended at least monthly for the first 3 months of treatment to support medication-taking behavior by assessing efficacy, managing adverse effects, and monitoring health status. Adverse effects from obesity medications are more likely to occur at initiation and with dose escalations (60,61), and frequent contact with the health care team may help support individuals

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experiencing these effects. Table 2.1 includes strategies on how to manage common adverse effects for each obesity medication; health care professionals should also develop a differential diagnosis for significant adverse effects and exclude other potential causes or contributors to the symptoms. Unless clinical circumstances (such as poor medication tolerability) or other considerations (such as financial expense) suggest otherwise, individuals who achieve sufficient early weight reduction with an obesity medication (typically defined as ≥5% weight reduction after 3 months) should continue the medication long term. Modeling from clinical trials shows that early responders have improved long-term outcomes (244,245). When early weight reduction results are modest, the benefits of ongoing treatment need to be examined in the context of dose-escalation progress, treatment tolerance, improvements in obesity-related diseases and complications, the availability of other treatment options, and overall treatment burden. During this initial period, follow-up can be delivered via telehealth with interprofessional team members to facilitate timely and effective care. An RCT evaluating the comparative effectiveness of a behavioral weight-reduction intervention found that both in-person and remotely delivered interventions led to significant weight reduction compared with control and that the weight change did not differ significantly between the two intervention groups (246). Real-world evidence also supports the use of telehealth care delivered by clinical practices, which achieves similar outcomes to in-person visits (247–249).

After this initial 3-month period, regular follow-up care with individuals on obesity medications is needed to continue monitoring the efficacy and safety of the treatment plan. Real-world data from an academic obesity medicine clinic found that a greater number of follow-up visits was associated with greater weight reduction (150), which underscores the importance of regular interaction between individuals with obesity and health care professionals. Health care professionals should arrange for follow-up at least every 3 months for the remainder of the first year of treatment and plan for follow-up at least every 6 months for long-term management. Ongoing monitoring of the achievement and maintenance of treatment and weight-reduction goals is recommended. For individuals not reaching or maintaining treatment goals, treatment inertia should be avoided by reevaluating ongoing obesity therapies and intensifying treatment with additional approaches. Shared decision-making should be used to determine the best long-term obesity treatment approach. See the section above on Long-term Management of Obesity Medications for additional information.

Health care teams should be knowledgeable about health insurance formularies and obesity medication coverage requirements, as well as eligibility for medication assistance programs, copayment reduction cards, and direct-to-consumer cash pay options. Clinical practices should anticipate that most prescriptions for obesity medications will require prior authorization. U.S. health care professionals have reported that prior authorization alters their prescribing behaviors generally (250). A systematic review (46 studies) found that prior authorization and step therapy requirements were associated with lower medication use, which negatively affected medication-taking behaviors and clinical outcomes (251). Therefore, clinical practices should consider allocating resources to manage prior authorizations for obesity medications. Pharmacists or pharmacy technicians may also be able to assist with this process. Given that insurance coverage and costs may influence treatment decisions, payors should cover evidence-based obesity medications, particularly for people with obesity-related diseases and complications, to improve access and outcomes. Real-world research found that individuals who combined obesity medication with an intensive lifestyle program were significantly more likely to achieve clinically significant weight reductions and improve cardiometabolic markers (e.g., blood pressure and A1C) at 6, 12, and 24 months as compared with an intensive lifestyle program alone (166). Notably, the individuals prescribed obesity medication with the program also had fewer inpatient hospitalizations and emergency department visits than those who completed the lifestyle program alone, which resulted in lower medical costs.

Conclusions

Stakeholders, including individuals with obesity, health care professionals, policy makers, insurers, and employers, increasingly recognize the need for safe and effective pharmacotherapy to treat obesity. The ADA's Obesity Association encourages health care professionals to adopt and implement the present recommendations on obesity medications as part of a comprehensive obesity treatment plan for adults. Evidence supports the use of obesity medications in combination with lifestyle interventions to achieve long-term health and weight reduction goals. Obesity medications should be discussed with all individuals with obesity, and treatment plans for individuals with obesity who have or are at high risk of obesity-related diseases and complications should prioritize use of obesity medications with demonstrated benefit in improving the individuals' obesity-related diseases. Given the various pharmacologic approaches now in development, additional obesity medications are likely to come to market in coming years that may further expand treatment options.

Appendix

American Diabetes Association Professional Practice Committee for Obesity. Committee members include Kimberly A. Gudzune,||*** Caroline M. Apovian, Vanita R. Aroda, Louis J. Aronne,*** Kirthikaa Balapattabi,** Allison K.

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DUALITY OF INTEREST

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AUTHOR CONTRIBUTIONS

The development of these clinical guidelines involved contributions from all listed individuals of the American Diabetes Association Professional Practice Committee for Obesity (K.A.G., C.M.A., V.R.A., L.J.A., K.B., A.K.B., S.C., N.A.E., A.F., S.L.F., W.T.G., S.H., S.K., K.K., R.F.K., J.J.N., J.W.O., E.J.P., L.P., A.P.S., F.C.S., and R.R.B.) in the planning, conduct, and reporting of the work. All subcommittee members contributed to conception and design, conduct, acquisition of data or analysis, and interpretation of data and contributed to planning and drafting of the manuscript. All committee members contributed to conception, planning, and data interpretation and reviewed the manuscript and provided critical feedback. The American Diabetes Association Professional Practice Committee for Obesity collaboratively reviewed and approved the final guidelines. R.R.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All contributors have provided their consent for inclusion in this statement.

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